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PLASMA PROTEIN STUDIES ON NORMAL NEWBORN AND PREMATURE INFANTS

I. Plasma Protein Values for Normal Full Term and Normal Premature Infants
II. Use of Concentrated Normal Human Serum Albumin in Treatment of Premature Infants

LUCY-GALE McMURRAY, M.D.
PASADENA, CALIF.
AND
JOSEPH H. ROE, M.D.
AND
LEWIS K. SWEET, M.D.
WASHINGTON, D. C.

HYPOPROTEINEMIA in newborn and premature infants has been noted by several investigators.[1] These studies, however,

This study was supported by a grant from the Milbank Memorial Fund.

From the Department of Pediatrics, Gallinger Municipal Hospital, and the Departments of Pediatrics and Biochemistry, George Washington University Medical School.

The albumin ("normal serum albumin [human] concentrated") used in these studies was developed from blood collected by the American Red Cross and produced under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University. The use of this material was authorized by the Naval Medical School, Bethesda, Md.

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(Footnote continued on next page)

have not correlated exactly the weight at birth and the degree of hypoproteinemia, nor have they demonstrated serially the levels of the blood proteins observed over a period of time in the same infants. Recently, when the products of fractionation of human plasma became available for study,[2] it seemed that there might be possible advantage in the use of concentrated normal human serum albumin for premature infants, particularly if repeated determinations for such infants demonstrated little or no increase in the plasma proteins. In order to define the problem more clearly, we decided to recheck the values for plasma proteins in both normal full term and normal premature infants, to follow carefully over a period of time the protein values observed for a number of small premature infants and then to evaluate carefully a small group of premature infants whose general treatment was identical except that alternate infants were given concentrated normal human serum albumin intravenously. The purpose of the present paper is to report the results of this study.

METHODS OF PROTEIN DETERMINATION

Plasma was used in these studies, as it proved easier to obtain nonhemolyzed plasma than serum when blood was being taken from small infants. Clear, nonhemolyzed plasma was used in all determinations, since hemolysis, however slight, causes abnormally high readings with the methods used. A modification of the Kingsley method,[3] in which advantage was taken of the Greenberg procedure[4] for separating globulins from albumin, was used in these determinations. This method was preferred because it required no more than 2 cc. of blood from the infant. Carefully calibrated pipets and apparatus were used throughout.

The total protein values were detemined as follows: One-tenth cubic centimeter of plasma was pipetted into a 100 cc. volumetric flask. Approximately 50 cc. of water was then added. To this was added 4 cc. of five times normal sodium hydroxide, followed by 6 cc. of Folin's phenol reagent.[5] This solution was made

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up to volume, mixed thoroughly and allowed to stand fifteen to thirty minutes before being read in a Klett-Summerson photoelectric colorimeter. A no. 54 green filter, which transmits light with a wavelength of 500 to 570 millimicrons was used in the colorimeter. With this method the intensity of the color was observed to increase for fifteen minutes and then to remain constant up to thirty minutes.

The albumin and globulin fractions were determined as follows: Warm 22.5 per cent solution of sodium sulfate, 9.5 cc., was placed in a centrifuge tube, and 0.5 cc. of plasma was added. This mixture was well shaken, and 3 cc. of ether was added. After vigorous shaking, the tube was stoppered and centrifuged five to ten minutes. The precipitated globulins separated into a compact layer between the ether phase and the sodium sulfate solution. Two cubic centimeters of the aqueous centrifugate was removed and placed in a 100 cc. volumetric flask. This removal was facilitated by tilting the centrifuge tube to allow the pipet to pass through the ether phase and under the globulin layer, while a finger was held over the end of the pipet. To this solution were added approximately 50 cc. of water, 4 cc. of five times normal sodium hydroxide and 6 cc. of Folin's phenol reagent. The contents of the flask were then made up to volume and mixed, and the solution was read in the colorimeter fifteen to thirty minutes later. The value obtained was the albumin content.

The layer of globulin precipitate and the remaining albumin solution were then filtered. The globulin precipitate was thoroughly washed with warm 22.5 per cent solution of sodium sulfate to remove any remaining albumin. The filtrate and washings were discarded, and the funnel, with the filter paper containing the precipitate, was transferred to a 100 cc. volumetric flask. Four cubic centimeters of five times normal sodium hydroxide was added, and a hole was punched in the filter paper with a glass rod to let the solution run through freely. The filter paper was washed carefully with water until all the dissolved globulin and the traces of precipitate were removed into the flask. Water was added as needed to bring the volume up to 50 cc., and 6 cc. of Folin's phenol reagent was added. The solution was made up to volume with distilled water, mixed thoroughly and read in the colorimeter fifteen to thirty minutes later.

A reagent blank containing all materials except the plasma itself was made up each day and used to set the colorimeter at zero.

Calculations.—The following equations were used:

Total proteins: $\frac{RU}{RS} \times 0.001 \times \frac{100}{0.1} \times 16.0 =$ Grams total protein per 100 cc. of plasma

Albumin: $\frac{RU}{RS} \times 0.001 \times \frac{100}{0.1} \times 16.8 =$ Grams albumin per 100 cc. of plasma

Globulin: $\frac{RU}{RS} \times 0.001 \times \frac{100}{0.5} \times 14.4 =$ Grams globulin per 100 cc. of plasma

In these equations: *RU* indicates reading of the unknown; *RS*, reading of the standard; 0.001, amount (Gm.) of tyrosine in 5 cc. of standard solution; $\frac{100}{0.1}$, $\frac{100}{0.5}$, 0.1 cc. or 0.5 cc. of plasma used; 16, factor for converting value for tyrosine into total protein; 16.8, factor for converting value for tyrosine into albumin, and 14.4, factor for converting value for tyrosine into globulin.

This method was carefully studied in the laboratory before clinical application was made. Calibration curves showing straight line values within the ranges covering the amounts of tyrosine used for total proteins, albumin and globulin were made. These curves were checked against the original tyrosine standard at frequent intervals. Duplicate determinations of the albumin and total protein contents were made on each sample of plasma. The globulin fraction was deter-

mined from a single analysis. In the data presented, the sum of the albumin and globulin fractions separately determined was found to equal the total protein value within close limits (93 to 107 per cent). This figure, we think, is an important check in plasma protein studies. Such an analytic procedure gives a reliable check on the values obtained and avoids the danger of including an inaccurate determination of a single fraction which is inherent in calculating the plasma protein partition by sum or difference methods.

I. PLASMA PROTEIN VALUES FOR NORMAL FULL TERM AND NORMAL PREMATURE INFANTS:

During the first week of life, determinations of total proteins, albumin and globulin were made from one to three times on each of 78 infants whose weights at birth varied from 3 pounds 8 ounces to 8 pounds 8 ounces (1,588 to 3,856 Gm.). In table 1 the values for plasma protein have been correlated with the weight at

TABLE 1.—*Values for Plasma Protein for Seventy-Eight Newborn Infants During the First Week of Life*

Weight at Birth of Infants	Albumin			Globulin			Total Protein		
	No. of Determinations	Mean Value, Gm./100 Cc.	Standard Deviation *	No. of Determinations	Mean Value, Gm./100 Cc.	Standard Deviation *	No. of Determinations	Mean Value, Gm./100 Cc.	Standard Deviation *
3 lb. 8 oz. to 3 lb. 15 oz....	12	4.7†	0.55	13	1.45	0.45	13	5.57	0.58
4 lb. to 4 lb. 7 oz.....	19	4.2	0.57	18	1.67	0.29	22	5.5	0.41
5 lb. to 5 lb. 7 oz.....	6	4.3	0.33	6	1.66	0.46	6	5.8	0.44
Total premature infants	37	4.3‡	0.60	36	1.60	0.37	41	5.6‡	0.47
5 lb. 8 oz. to 6 lb. 7 oz.....	15	4.7	0.55	17	1.69	0.55	16	6.3	0.66
6 lb. 8 oz. to 7 lb. 7 oz.....	17	4.7	0.59	18	1.88	0.44	18	6.4	0.74
7 lb. 8 oz. to 8 lb. 7 oz.....	14	4.8	0.39	15	1.67	0.54	16	6.4	0.41
Total full term infants..	46	4.8‡	0.47	50	1.75	0.49	50	6.4‡	0.60

* Standard deviation is calculated by taking square root of the variance.

† The values for albumin for these small infants probably are not reliable, as it was extremely difficult to secure clear, nonhemolyzed serum from them.

‡ The differences between the mean values for albumin and for total protein are significantly higher for full term infants than for premature infants when tested by the method of t. For total protein, t = 6.5; for albumin, t = 4.0.

birth. The infants were divided into six groups according to weight. Each of the three groups of premature infants covered a range in weight of 8 ounces (227 Gm.); each of the three groups of full term infants covered a range in weight of 1 pound (454 Gm.). Infants who weighed between 4 pounds 8 ounces and 5 pounds (2,141 to 2,268 Gm.) were inadvertently missed in this study. Thirty-nine premature infants were studied. There were 13 in the group with the lowest weights, 20 in the next group and 6 whose weights were between 5 pounds and 5 pounds 8 ounces (2,268 and 2,495 Gm.). Thirty-nine full term infants were studied. Of these infants, there were 13, 14 and 12 in the three groups, respectively.

The albumin content of the plasma was significantly higher in full term than in premature infants (table 1, column 1). When the mean value for all albumin determinations made on full term infants (4.8 Gm. per hundred cubic centimeters) is compared by the method

of t[6] with the mean value for all the determinations on premature infants (4.3 Gm. per hundred cubic centimeters), the difference, statistically, is definitely significant ($t = 4.0$). Furthermore, the mean concentration of plasma albumin obtained for the premature infants who weighed 4 pounds to 4 pounds 7 ounces (1,814 to 2,013 Gm.), inclusive (the smallest infants on whom absolutely reliable determinations could be made) was significantly lower that the mean albumin concentration obtained for any or all groups of full term infants ($t = 2.6$, 2.6 and 3.4 respectively). The group of premature infants whose weights were over 5 pounds (2,268 Gm.) showed a mean concentration of plasma albumin that was lower than the one determined for infants weighing 7 pounds 8 ounces (3,412 Gm.) or over ($t = 2.5$), but it was not significantly different from the mean value for any other group of infants studied.

The group of premature infants whose weights at birth were between 3 pounds 8 ounces and 3 pounds 15 ounces (1,588 and 1,786 Gm.) had a mean albumin concentration that was equal to the one observed for full term infants and was significantly higher than the mean concentration found for the group of next larger premature infants ($t = 2.4$). These values may have been too high, owing to hemolysis that was not discernible to the unaided eye. It was extremely difficult to obtain clear serum from these infants. For this reason, these figures must be confirmed before they can be accepted.

The average concentration of plasma albumin of normal full term infants (4.8 Gm. per hundred cubic centimeters) is within the normal adult range of 4.5 to 6.5 Gm. per hundred cubic centimeters. The average value for premature infants (4.3 Gm. per hundred cubic centimeters) is below the normal adult values. The range of values for plasma albumin for premature and for full term infants is no greater than that for normal adults.

The globulin values (table 1, column 2) showed a slight rise with the increasing maturity of the baby, but the difference of the means for no two groups was significant. In all cases the values for t was less than 2. In all our patients the mean globulin values were within the normal adult range. (Normal adult values for globulin are 1.2 to 2.2 Gm. per hundred cubic centimeters.)

The total protein content of the plasma (table 1, column 3) is a reflection of the sum of the contents of albumin and globulin. The

6. Davenport, C. B., and Ekas, M. P.: Statistical Methods in Biology, Medicine and Psychology, New York, John Wiley and Sons, Inc., 1936, page 37. Values for t (the quotient obtained by dividing the difference of the two means by the standard deviation of the difference of the two means) of 2.0 or above indicate a probability of chance causing the variation in 2.5 per cent or less and are considered to indicate statistical significance.

mean value for all determinations for premature infants (5.6 Gm. per hundred cubic centimeters) was significantly lower than the mean value for all determinations for full term infants (6.4 Gm. per hundred cubic centimeters) when computed by the method of t ($t = 6.5$). Furthermore, the mean value for total protein for the two groups of premature infants whose weights were 4 pounds 7 ounces (2,013 Gm.) or less was significantly different from the mean values for all groups of full term infants (t varied from 3.0 to 6.6). The mean value for the larger premature infants was significantly lower than the mean total protein value for the full term infants whose weights at birth were 7 pounds 8 ounces (3,412 Gm.) or over ($t = 3.0$), but the difference for the mean value obtained from the plasma of the other two groups of full term infants was not significant ($t = 1.6$ and 1.8). There was no significant variation between the mean values obtained for any two groups of premature infants or between those obtained for any two groups of full term infants.

II. USE OF CONCENTRATED NORMAL HUMAN SERUM ALBUMIN IN TREATMENT OF PREMATURE INFANTS

PLAN OF STUDY

For the purpose of this study, 33 normal, healthy newborn premature infants whose weights at birth were between 3 pounds 8 ounces and 4 pounds 8 ounces (1,588 and 2,141 Gm.) were used. No infant with any evident congenital abnormality was included in this group. Otherwise, all infants with weights at birth within this range who were cared for in the nurseries for premature infants between Oct. 1, 1945 and May 1, 1946, were included in the study. Of the infants, 30 were born in the hospital, and 3 were brought to the hospital within a few hours of birth.

The general management, diet and nursing care of these infants were similar. The diet was composed of evaporated milk, corn syrup and water. The caloric intake was increased gradually to a daily average of 60 per pound (0.5 Kg.) at the end of the third week. Thereafter, the caloric intake remained at approximately 60 per pound per day. This diet gave a protein intake of approximately 2.2 Gm. per pound (4.8 Gm. per kilogram) per day. The single variation in the care of these infants was that 16 infants (including 2 of the 3 who were born outside the hospital) were given repeated intravenous injections of concentrated normal human serum albumin (containing 25 Gm. of albumin per hundred cubic centimeters). In actual fact, the albumin was not given strictly to alternate infants. In the beginning of the study serial determinations of the plasma proteins were undertaken to establish the normal values with increasing age and weight of the infants. It was after the irregular and erratic values were demonstrated that it was decided to proceed with the second portion of the study, administering albumin in an effort to obtain more stable results, and determining the possible effects on the growth of the infants. When this decision was reached, 10 infants had been admitted to the study without being given albumin. Thereafter, the infants were admitted alternately to the treated and to the control groups until the last month of the study, when 5 consecutive infants were admitted to the treated group of patients. (A few infants who had been admitted to the study at birth were excluded later when congenital defects became apparent.)

Determinations of plasma protein were made by the technics described previously for each infant twenty-four to thirty-six hours after birth. For those not receiving albumin repeat determinations were made once a week until the infant was discharged on reaching a weight of 5 pounds 8 ounces (2,495 Gm.). The infants receiving albumin intravenously were tested at various intervals in this study. Initial determinations were made between twenty-four and thirty-six hours of life, before any albumin was given. The first injection of albumin was given on the third or fourth day of life. Subsequent determinations of plasma protein were carried out one to four times each week throughout the period of hospitalization.

Determinations on the first 3 infants in this group were made three to four times weekly throughout their entire stay in the hospital. These infants received 2 cc. of concentrated normal human serum albumin per pound intravenously, and blood was drawn one, two and twenty-four hours after each injection to determine the peak of the protein values. There were slight differences in the results of these determinations. Thereafter, for all succeeding infants the samples of blood were drawn one hour after the administration of albumin.

The next 4 infants were tested two to three times weekly, as it was felt there was too little variation in the values for plasma protein for the first 3 infants to warrant continuation of the more frequent sampling. The quantity of albumin given was changed midway in the study of these 4 infants from 2 to 3 cc. per pound per injection. A pronounced increase in the rapidity of the rise of total protein and albumin was noted after this change, and the general condition of the infants appeared to improve. All remaining infants received 3 cc. of albumin per pound of body weight at each injection.

The frequency with which the albumin was given was again reduced, and the next 4 infants were given albumin twice weekly from birth to the third or fourth week of life, or until a definite rise and stabilization in the protein values were apparent. After this period, they received albumin only once a week. The next 3 infants in the group received albumin twice weekly for two weeks, followed by one weekly injection thereafter. The last 2 infants in the group received albumin only once a week throughout.

RESULTS

The results of the serial determinations of the plasma protein are shown in charts 1 through 5. Charts 1 and 3 show the values obtained for those infants who were given albumin; charts 2 and 4, for the control infants. In each of these four charts the results of the individual determinations, as well as the mean values, are shown. The infants who received albumin showed not only a steady, progressive rise in plasma albumin and total protein values but also a narrower, less variable range of values. Chart 5 shows for both treated and control infants the variations in the mean values for total protein and both fractions with the increasing age of the infants. The progressively higher and more stable albumin values of the infants who were given albumin is obvious (table 2).

From the third week on there was a significant statistical difference in the mean values obtained for plasma albumin. (The values for t, beginning with the third week, were 3.7, 2.0, 3.5, 2.5, 2.35, 2.86 and 3.7, respectively.) There was a statistically significant drop in the

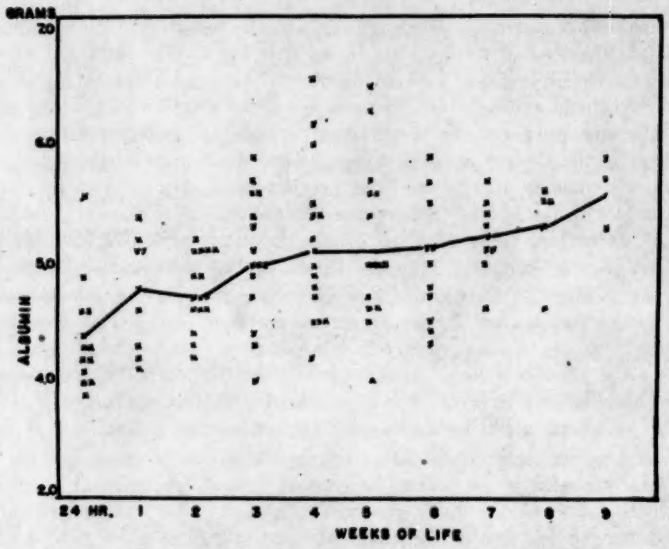

Chart 1.—Serial values for plasma albumin obtained for 16 normal premature infants who were given concentrated normal human serum albumin intravenously.

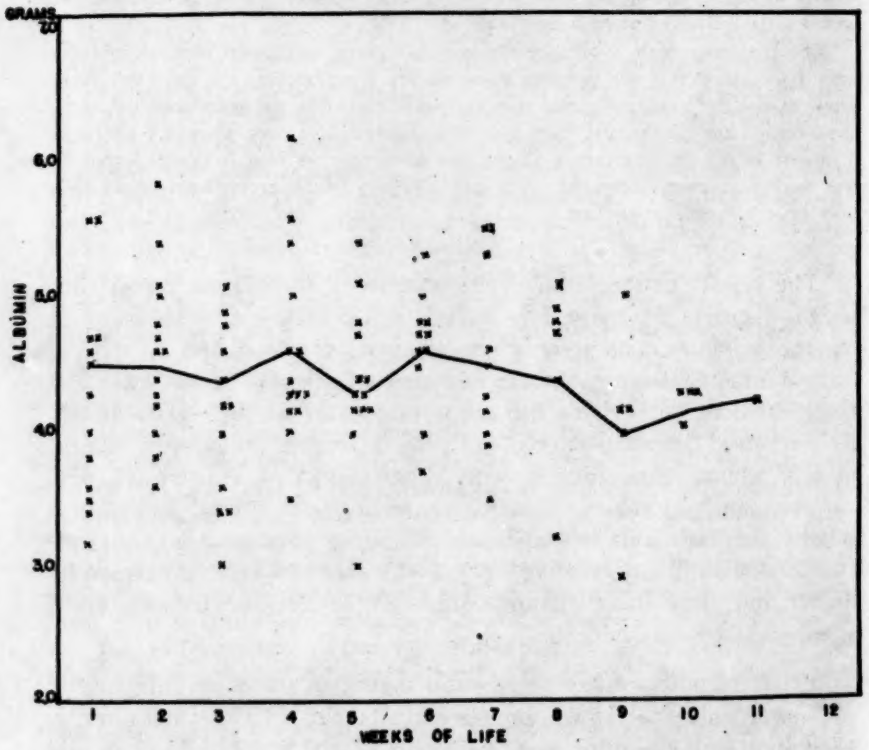

Chart 2.—Serial values for plasma albumin obtained for 17 normal premature infants.

mean value for globulin for the infants who were given albumin after the first such injection ($t = 2.1$). Thereafter, the mean globulin values for these infants were consistently lower than the values for those to whom no albumin was given. These differences were not statistically significant at various age periods, but when the means of

TABLE 2.—*Mean Serial Values for Plasma Albumin for Thirty-Three Premature Infants, Sixteen of Whom Were Given Normal Human Serum Albumin Intravenously*

	Infants Given Albumin			Infants Not Given Albumin			
Age, Weeks	No. of Infants	Mean Value for Albumin, Gm./100 Cc.	Standard Deviation	No. of Infants	Mean Value for Albumin, Gm./100 Cc.	Standard Deviation	Value for t*
Before albumin was given							
1	13	4.4	0.45	13	4.5	0.86	0.4
After albumin was given							
1	7	4.8	0.50	..	...	....	...
2	16	4.7	0.30	15	4.5	0.50	1.1
3	16	5.0	0.61	14	4.1	0.62	3.7
4	16	5.1	0.62	16	4.6	0.70	2.0
5	15	5.1	0.62	16	4.3	0.58	3.5
6	12	5.1	0.68	11	4.5	0.53	2.5
7	9	5.3	0.34	10	4.5	0.75	2.35
8	5	5.4	0.45	8	4.4	0.61	2.86
9	3	5.7	0.20	5	4.0	0.79	3.7
10	0	...	....	4	4.3	0.22	...
11	0	...	....	2	4.4	0.00	...

* The value for t is the quotient of the difference of the two means divided by the standard deviation of the difference of the two means.

TABLE 3.—*Comparisons of the Time Required to Regain Weight at Birth and to Reach Normal Discharge Weight and of the Morbidity and Mortality Rates of Premature Infants Who Received Concentrated Normal Human Serum Albumin Intravenously, With Similar Data on Control Infants*

	Living Infants							
		Weight at Birth Regained, Days		Days in Hospital		Illnesses		
	No. of Infants	Average	Standard Deviation	Average	Standard Deviation	None	Mild	Severe	Deaths
With albumin	16	17.9	5	49.0	9	12	4	0	0
Without albumin	17	26.4	13	56.8	15	5	7	4	2

all determinations made after one or more injections of albumin (1.27 Gm. per cent for 95 samples) were compared with the mean of all determinations made on the control infants (1.50 Gm. per cent for 121 samples), the difference was definitely significant ($t = 5.0$). The differences in mean values for total protein are the sum of the differences for albumin and for globulin.

The clinical results of this treatment are shown in chart 6 and table 3. Chart 6 shows the individual weight curves for the 33 infants and gives a picture of the progress of each infant. Those infants who

received albumin showed a more rapid gain in weight, with only 4 remaining over six weeks in the hospital. Of these, 2 were the infants who received 3 cc. of albumin solution per pound only once a week. In contrast, there were 6 infants in the control group who remained in the hospital over six weeks, the longest stay being eleven weeks for each of 2 infants.

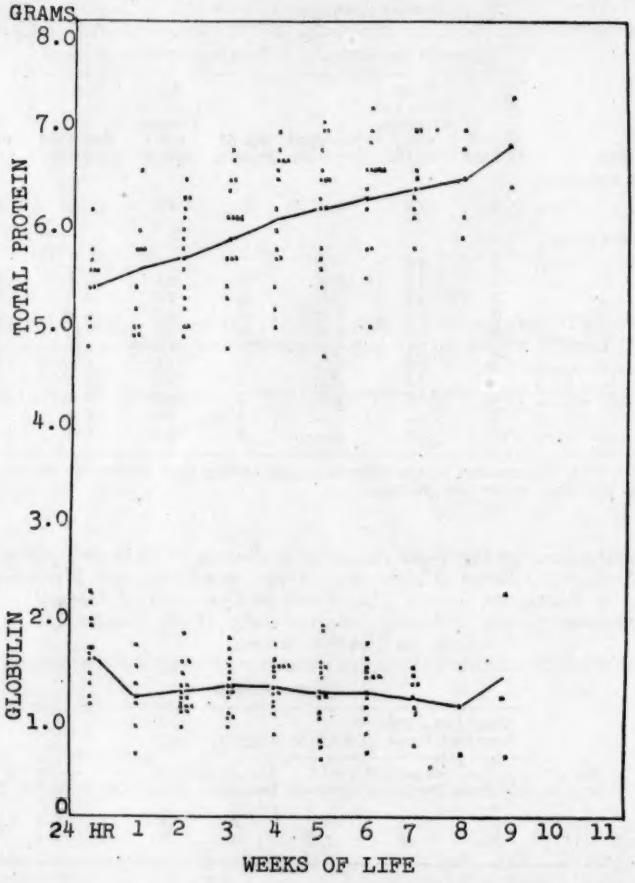

Chart 3.—Serial values for plasma globulin and total protein obtained for 16 normal premature infants who were given concentrated normal human serum albumin intravenously.

As is shown in table 3, the health of the infants who were given albumin was much better than that of the control infants. There was no severe illness or death among the former, and only 4 instances of mild gastroenteritis, whereas among the latter infants there were 2 deaths, with 4 severe and 7 mild illnesses among the infants who survived. The 2 infants who died were the smallest in the group, and

their inclusion might be fortuitous. The infants who received albumin required a shorter time to regain the weight at birth and to reach the normal weight at discharge than those who did not. The difference was statistically significant for regaining of the weight at birth ($t = 2.4$), but not for reaching the weight for discharge ($t = 1.8$). It is further

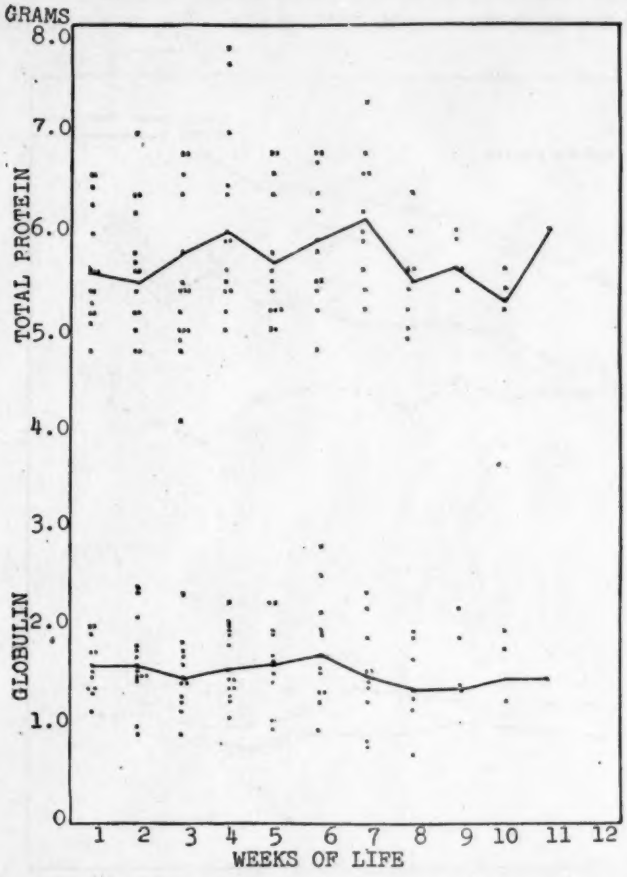

Chart 4.—Serial values for plasma globulin and total protein obtained for 17 normal premature infants.

of considerable significance that the nurses commented frequently on the greater vigor and better general appearance of the treated infants.

Subsequent follow-up data on 16 of these infants were gathered by checking the records of the municipal child welfare centers from which the care in the home was supervised. This group included 10 infants who received albumin and 6 who served as controls. At 3 and 5 months of age the babies who received albumin continued to show

a uniform advantage when gaged by weight. In no infant who had received albumin did any jaundice develop within the period of the follow-up study.

COMMENT

The number of infants observed in this study is too small to permit final conclusions as to the value of concentrated normal human serum albumin in the treatment of premature infants. The results as indicated

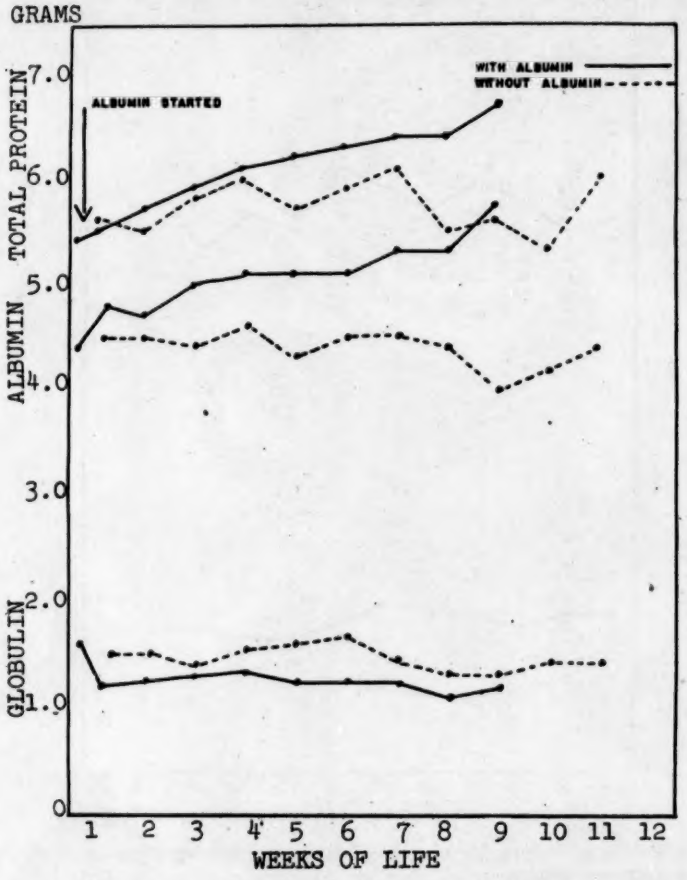

Chart 5.—Mean serial values for plasma albumin, globulin and total protein obtained for 16 normal premature infants who were given concentrated normal human serum albumin intravenously and for 17 similar control infants.

are extremely suggestive, however, and certain tentative observations as to the schedule of administration are valid. Because of the high osmotic pressure and the consequent dehydrating effect of the albumin, the first injections were 2 cc. per pound of body weight. When these injections were repeated three times a week, there was a slow increment of plasma albumin and total protein, and there was no evident deleterious effect from dehydration. Therefore, in order to accelerate the protein

increases, the individual injections were increased to 3 cc. per pound of body weight. These were well tolerated, and the increase of plasma albumin and total protein was more rapid. There was no adverse reaction to any injection of the albumin. The optimum results apparently were obtained in the small group of infants who received 3 cc. per pound of body weight, with injections given twice a week for three

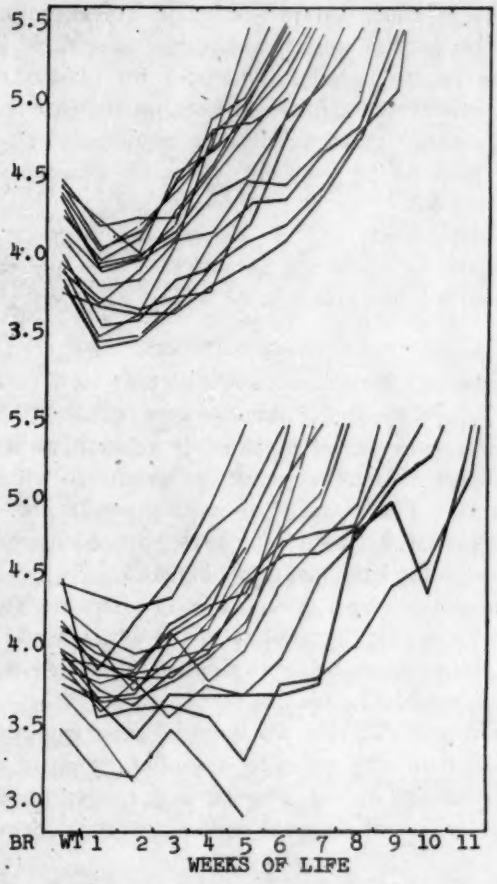

Chart 6.—Individual weight curves of 16 normal premature infants who were given concentrated normal human serum albumin intravenously (upper portion), and of 17 similar control infants (lower portion).

or four weeks (depending on the albumin content of the plasma) and weekly thereafter. This schedule appears to allow maximum results with minimum trauma from the handling of the infants. Much larger injections have been given to infants with edema.[7]

7. Jacobi, M.; Litvak, A., and Gruber, S.: The Influence of Human Serum Albumin on Edema in Erythroblastosis Fetalis, J. Pediat. **29**:177, 1946.

We have no knowledge at present as to the actual mode of action of albumin administered intravenously. Since the number of calories introduced is so small (the albumin solution gives approximately 1 calorie per cubic centimeter), it is improbable that that added caloric intake is of major significance. However, the amount of protein injected was considerably more than that retained in the circulating blood. This difference would suggest that the presynthesized protein was used rapidly in tissue production or in building up body stores of protein, and this process might explain the more rapid growth.

The decrease in the globulin content of the plasma has not been explained. This decrease might be due to an increase in the volume of circulating blood, to a greater deposition of albumin or to a decreased manufacture of globulin by the body when the deficiency of albumin was partially corrected. The clinical results indicate that the decrease of globulin in the plasma had no deleterious effect on the infants' resistance to infection, inasmuch as infection was present less often and, when present, was less severe in the infants who were given albumin.

SUMMARY

Determinations of the albumin, globulin and total protein contents of the plasma of 78 newborn infants were made. There was no significant difference in values obtained in relation to the weights at birth of the infants within the premature group or within the group of mature infants. There was, however, a significant difference in the values for albumin and total protein determined for premature and mature infants, with the latter definitely higher.

Serial determinations on a group of small premature infants showed a wide range, with erratic fluctuations of the albumin and total protein contents of the plasma, there being no significant increase with increasing age and development of the infants.

When concentrated (25 Gm. per hundred cubic centimeters) normal human serum albumin was given to a similar group of infants, there were a steady increase in the albumin and total protein contents of the plasma and an initial decrease with subsequent lower values for globulin.

Infants who were given albumin made a more rapid gain in weight and had fewer illnesses than did similar infants who received no albumin. The advantage imparted to these infants during their stay in the hospital was maintained at 3 and at 5 months of age.

CONCLUSIONS

The use of concentrated normal human serum albumin in the care and treatment of premature infants appears to be advantageous and merits further study.

129 North Hill Avenue (4) (Dr. McMurray).
1331 H. Street, N. W. (Dr. Roe).
Nineteenth Street and Massachusetts Avenue, S. E. (3) (Dr. Sweet).

LENGTHS OF THE FEMUR AND THE TIBIA

Norms Derived from Orthoroentgenograms of Children from Five Years of Age Until Epiphysial Closure

MARGARET ANDERSON, M.S.
AND
WILLIAM T. GREEN, M.D.
BOSTON

THE GROWTH of the femur and the tibia is an important consideration in clinical medicine, as well as in the assay of the development of the normal child. Unequal growth of the lower extremities occurs in many conditions, often to an extent requiring operative measures to correct the discrepancy. Surgical arrest of one or more of the epiphyses on the longer leg is the procedure of choice in many instances, the site of operation being ordinarily the lower part of the femur or the upper part of the tibia. Since each epiphysis contributes a specific percentage of the growth of the extremity, the timing of such an operation can be established if the amount of growth from the particular bone can be predicted.

We have been unable to find any published values for the lengths of the tibia and the femur which covered the adolescent years and which were applicable to our requirements. Standards are of limited value for indicating expected growth when they do not continue beyond the age of 12 or 14 years, when they are based on measurements of roentgenograms filmed with an inexact technic, or when they are derived from measurements of diaphysial lengths only.

We have now compiled sufficient material in a longitudinal study of six years' duration to warrant the presentation of preliminary averages, which we hope will serve as a useful guide for both the research worker and the practicing surgeon.

There are three major points which should be emphasized in discussion of the norms to be presented: First, the values given are based on semilongitudinal data and cover the period from 5 years of age until the cessation of growth in the lower extremities. Second, our values are

This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc.

From the Children's Hospital, the Department of Orthopedic Surgery of the Harvard Medical School and the Department of Maternal and Child Health of the Harvard School of Public Health.

based on skeletal rather than chronologic age. Third, the true length of each bone is given: a roentgenologic technic was employed which allowed the recording of the bone shadow without distortion, and our measurements included the epiphyses as well as the diaphyses.

MATERIAL

Of the 255 children on whom these values are based, 213, or 84 per cent, were enrolled in a study of the effects of poliomyelitis on the growth of the lower extremity at the Children's Hospital in Boston. Each of these children had one leg which was, to the best of our knowledge, normal in every respect, and only the measurements of this leg were included in our computations.

To augment and verify the data we included measurements from a group of normal children under study at the Department of Maternal and Child Health of the Harvard School of Public Health.[1] From the 300 children in this series, we selected the 42 whose data were strictly longitudinal and covered the longest span of years: in girls, this range extended from 5 through 13 years of age, and in

TABLE 1.—*Number of Children Whose Measurements Were Included in the Computation of Average Lengths of Femur and Tibia*

	Groups Showing Normal Maturation		Group Showing Irregular Maturation	Total
	A	*B*	*C*	
Boys	71	19	60	150
Girls	51	17	37	105
Total	122	36	97	255

In columns *A* and *B* are children exhibiting normal maturation; in *A* are listed the children enrolled in the study of growth following poliomyelitis, in *B*, the normal children from the Harvard School of Public Health. In column *C* are recorded the children from both groups (including 6 girls of the normal series) whose skeletal ages were used in computations because their rates of maturation differed consistently from the average.

boys, from 5 through 14 years; a few of these children had complete records through 15 years of age.

The average bone lengths derived from roentgenograms of the leg in these two series of children, the normal group and that composed of the patients who had had poliomyelitis affecting the leg opposite the one measured, showed no statistically significant difference at any age level. Measurements from both groups were therefore combined in forming the tables to be described.

In analyzing the material, one further subdivision was made (table 1). Those children, whether from the normal or the poliomyelitis series, who showed irregular rates of maturation were placed in a third group, group C, and their measurements were used after their ages had been adjusted on the basis of relative skeletal maturity. This group will be discussed later in detail. Thus, the total number of available subjects includes those in group A, which is made up of the patients in the poliomyelitis series who had normal skeletal ages throughout, those in group B, which represents the children in the normal series who also exhibited consistently normal rates of maturation and those in group C, which was just described.

A distribution of the measurements used according to this grouping of the children involved is given in table 2. The largest number of roentgenograms (68 per

1. This general study of growth and development is under the direction of Dr. Harold C. Stuart.

cent) were of patients enrolled in the study of growth following poliomyelitis. No one group, however, contributed to the combined averages a constant proportion of the measurements at each age: below the age of 9 years, the majority of measurements were from the normal group; after this age, more were drawn from the other series. The number of children with irregular rates of maturation varied at each age level, but they contributed, in all, about one third of the total measurements included. This variation in the quantity of material provided by each group,

TABLE 2.—*Number of Measurements at Each Age Level Used in Computation of Averages*

Femur

Skeletal Age, Yr.	Boys				Girls			
	A*	B	C	Total	A	B	C	Total
5	2	19	1	22	3	17	0	20
6	5	19	4	28	5	17	0	22
7	8	19	5	32	11	17	0	28
8	15	19	7	41	16	17	0	33
9	29	19	11	59	24	17	10	51
10	38	19	14	71	25	17	16	58
11	47	19	18	84	29	17	22	68
12	45	19	23	87	27	17	26	70
13	36	19	32	87	25	17	28	70
14	33	19	37	89	17	12	29	58
15	25	4	36	65	15	8	26	49
16	16	0	31	47	13	0	20	33
17	13	0	26	39	..	..	..	..
18	12	0	25	37	..	..	..	..
Total	324	194	270	788	210	173	177	560

Tibia

Skeletal Age, Yr.	Boys				Girls			
	A*	B	C	Total	A	B	C	Total
5	2	19	2	23	3	17	0	20
6	5	19	5	29	5	17	0	22
7	8	19	6	33	10	17	0	27
8	15	19	7	41	14	17	0	31
9	28	19	9	56	18	17	10	45
10	35	19	12	66	17	17	14	48
11	40	19	13	72	18	17	17	52
12	34	19	20	73	16	17	20	53
13	30	19	26	75	18	17	22	57
14	27	19	31	77	13	12	24	49
15	25	4	33	62	10	8	21	39
16	16	0	29	45	9	0	15	24
17	13	0	23	36	..	..	..	..
18	12	0	23	35	..	..	..	..
Total	290	194	239	723	151	173	143	467

* For explanation of column headings, *A*, *B* and *C*, see footnote to table 1.

however, caused no alteration in the yearly distributions obtained other than that due to any increase in the available number of measurements.

The average number of roentgenograms used at each age level was 49, the smallest number being 20 and the largest, 89. The mean values were based on 1,348 measurements of the femur and 1,190 of the tibia (table 2). Fewer tibias were available for measurement because, in the series of children affected with poliomyelitis, the normal tibia was more frequently used for operative epiphysial arrest in an effort to equalize the lengths of the lower extremities. No child with less than three annual roentgenograms was included, the average for the total group being five roentgenograms at yearly intervals per child for each bone.

TECHNICS

The roentgenograms used were filmed by a special three exposure technic devised by us [2] which gives an accurate length of the entire lower extremity, from hip to ankle. Magnification of the shadow due to divergent roentgen rays is avoided in this method because the central ray is directed successively over each joint.

Roentgenograms in the series of normal children at the younger ages had been made with the use of the commoner "teleroentgenographic"

Fig. 1.—Orthoroentgenogram with the femur and tibia of one leg marked to show the landmarks used in the measurements of lengths.

method. Measurements from these roentgenograms were converted to orthoroentgenographic equivalents by the use of factors derived from a series of roentgenograms made by both methods on the same day.

Measurements of both bones were made to include the epiphyses (fig. 1). Their inclusion was necessary because in bones at the older

2. Green, W. T.; Wyatt, G. M., and Anderson, M.: Orthoroentgenography as a Method of Measuring the Bones of the Lower Extremities, J. Bone & Joint Surg. **28**:60-65 (Jan.) 1946.

age levels the epiphysial lines become irregular and later obliterated, so that roentgenographic measurements of the diaphyses alone are impossible. Femoral lengths were measured from the top of the capital

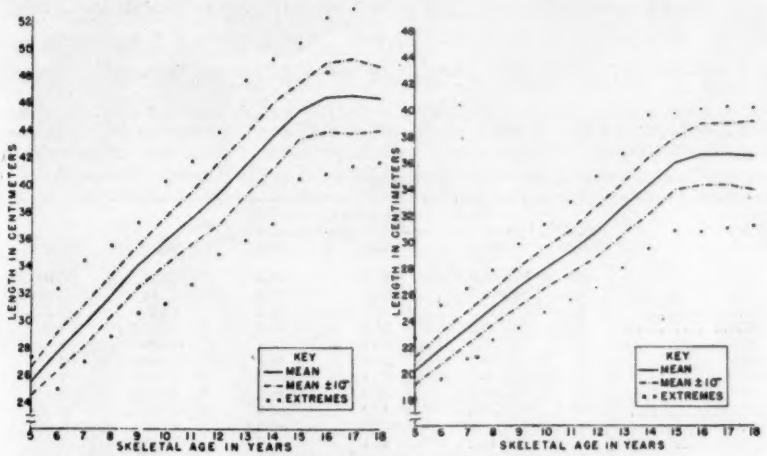

Fig. 2.—Average and extreme lengths of the normal femur, left, and of the normal tibia, right, derived from orthoroentgenograms of boys.

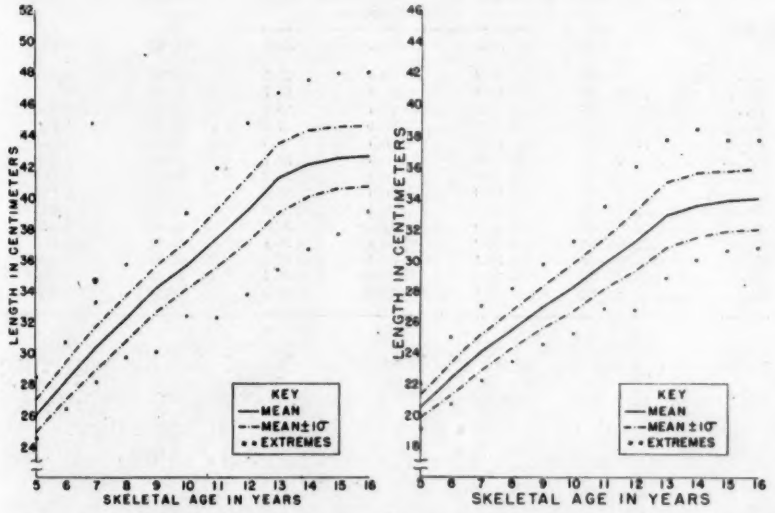

Fig. 3.—Average and extreme lengths of the normal femur, left, and of the normal tibia, right, derived from orthoroentgenograms of girls.

epiphysis to the most distal portion of the lateral condyle. Tibial lengths were measured from the midpoint of the line drawn through the upper margin of the condyles to the midpoint of the dense transverse line at the articular surface of the distal epiphysis. These measurements seemed

to express most effectively the weight-bearing length of the lower extremity, the dimension of importance in evaluating discrepancy in leg length.

The averages were constructed for skeletal age levels. Each child in the series was assessed according to the method outlined by Todd.[3] A child was considered to have "normal" maturation if his skeletal age was consistently within nine months of his chronologic age. If repeated

TABLE 3.—*Boys: Length of the Long Bones of the Lower Extremity in Centimeters*

		Femur				
		Percentiles				
Bone Age, Yr.	No. of Boys	10th	50th	90th	Mean	σ
5	22	24.2	25.6	26.8	25.52	1.042
6	28	26.0	28.0	29.2	27.74	1.485
7	32	27.8	29.8	31.6	29.68	1.536
8	41	29.6	32.1	33.6	31.80	1.496
9	59	31.8	34.1	36.1	33.96	1.582
10	71	33.7	35.7	38.2	35.80	1.832
11	84	35.1	37.4	40.0	37.50	1.878
12	87	36.6	39.3	42.2	39.31	2.310
13	87	38.5	41.2	43.9	41.41	2.188
14	89	40.2	43.5	46.8	43.48	2.402
15	65	42.6	45.4	47.7	45.33	2.041
16	47	42.8	46.6	49.4	46.27	2.503
17	39	42.6	45.8	49.6	46.40	2.556
18	37	42.9	45.8	49.4	46.16	2.361
		Tibia				
		Percentiles				
Bone Age, Yr.	No. of Boys	10th	50th	90th	Mean	σ
5	23	18.8	20.3	21.5	20.25	1.046
6	29	20.3	21.9	23.7	21.92	1.204
7	33	21.8	23.5	25.4	23.43	1.245
8	41	23.4	25.1	27.0	25.00	1.321
9	56	24.8	26.5	28.6	26.54	1.470
10	66	26.0	28.0	30.1	27.94	1.529
11	72	26.9	29.2	31.2	29.20	1.617
12	73	28.3	30.6	33.2	30.72	1.877
13	75	29.8	32.8	35.0	32.46	1.961
14	77	30.9	34.6	36.5	34.16	2.148
15	62	33.2	36.0	38.1	35.87	1.984
16	45	33.4	37.0	39.2	36.53	2.300
17	36	32.6	37.0	39.1	36.49	2.344
18	35	32.5	37.0	39.0	36.42	2.627

assessments during the years of observation showed that the maturation of the child was one, two or three years accelerated or retarded, his age was adjusted to correspond with his skeletal age rating. We included measurements only after any such necessary adjustments were made for the skeletal maturation of the individual child.

VALUES OBTAINED

Average values for the lengths of the femur and tibia are presented for boys and girls in both tabular and graphic form. The curves

3. Todd, T. W., and others: Atlas of Skeletal Maturation: Hand, St. Louis, C. V. Mosby Company, 1937.

depict the mean, the range of one standard deviation on either side of the mean and also the extreme lengths observed at each skeletal age level (figs. 2 and 3). The lengths obtained for the tenth, fiftieth and ninetieth percentiles show that, while the distributions are not perfectly symmetric, there is essentially no difference between the means and medians, except at the upper age levels where the number of children decreased and the observed variability increased (tables 3 and 4). Fewer children at the older ages were included because only 33 per cent

TABLE 4.—*Girls: Length of the Long Bones of the Lower Extremity in Centimeters*

Bone Age, Yr.	No. of Girls	Femur: Percentiles 10th	50th	90th	Mean	σ
5	20	24.7	26.1	27.6	25.98	1.087
6	22	26.7	28.2	30.2	28.18	1.216
7	28	28.6	30.2	32.6	30.31	1.412
8	33	30.6	31.9	34.6	32.19	1.453
9	51	32.4	34.0	36.1	34.12	1.501
10	56	33.4	35.6	37.7	35.65	1.582
11	68	35.0	37.4	40.1	37.44	1.881
12	70	36.3	39.2	41.9	39.20	2.084
13	70	38.0	41.2	43.9	41.18	2.225
14	58	39.5	41.8	44.4	42.06	2.093
15	49	40.3	42.3	44.8	42.44	1.981
16	33	40.1	42.3	45.4	42.54	1.889

Bone Age, Yr.	No. of Girls	Tibia: Percentiles 10th	50th	90th	Mean	σ
5	20	19.2	20.4	21.8	20.52	0.768
6	22	21.0	22.4	23.8	22.36	1.044
7	27	22.6	24.3	25.7	24.07	1.170
8	31	24.0	25.2	27.3	25.49	1.196
9	45	25.1	26.9	28.9	26.94	1.355
10	48	26.0	28.2	30.5	28.24	1.520
11	52	27.5	29.4	32.2	29.75	1.684
12	53	28.8	31.0	33.7	31.24	1.947
13	57	30.3	32.8	35.6	32.88	2.076
14	49	31.0	33.0	36.2	33.52	2.040
15	39	31.4	33.0	36.6	33.83	1.915
16	24	31.2	33.6	36.9	33.95	1.924

of those in the series had completed their growth in the lower extremities at the time of computation. The longitudinal nature of the material has served not only to give stability to the yearly averages but also, since data on each child appeared at three to eleven successive age levels, to insure the value of the curves obtained as patterns against which the growth of other children can readily be gaged and the lengths of their bones anticipated.

The ages given in the literature for the time of complete epiphysial closure for the femur and the tibia are widely varied. We have been able to examine the serial roentgenograms of 68 boys and 66 girls both before and after the termination of growth. The four epiphyses were observed to fuse within a few months of each other in a given child,

and fusion, as judged from the roentgenograms, was complete in boys at an average bone age of 17 years 3 months, and in girls, at 15 years 3 months. Inspection of the accompanying charts shows essentially the same thing, as well as the fact that significant growth appears to cease from twelve to eighteen months before these ages are reached.

Davenport [4] reported individual growth curves for boys which indicated that the femur grows slowly until the age of 11 to 12 years and then begins to grow rapidly, whereas the tibia grows rapidly until 13 to 14 years and thereafter at a greatly reduced rate. This difference in growth rates we have not observed either in our averages or in curves of

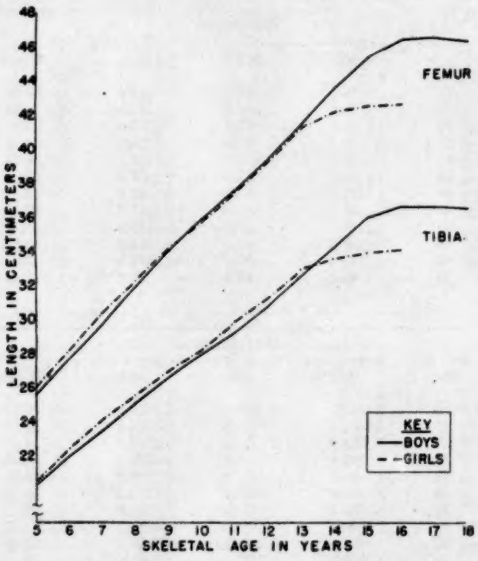

Fig. 4.—Mean lengths of bones for both boys and girls plotted on the same graph to show the similar values obtained at each age through 13 years if skeletal ages are used.

individual growth. The tendency appears to be for the proportion of growth between the femur and the tibia to remain fairly constant, although we have observed that often the femur grows a few months longer than the tibia, but the amount of such growth is insignificant.

In our series of children, it is noteworthy that there was essentially no difference between boys and girls in the mean lengths of the femur and tibia until the skeletal age of 13 years (fig. 4). Maresh [5] likewise observed little difference in the lengths of long bones for boys and for

4. Davenport, C. B.: The Crural Index, Am. J. Phys. Anthropol. **17**:333-353 (Jan.-March) 1933.

5. Maresh, M. M.: Growth of Major Long Bones in Healthy Children, Am. J. Dis. Child. **66**:227-257 (Sept.) 1943.

girls through the age of 12 years. While the averages for the boys and the girls were remarkably similar during this period, the tendency reported by Stuart and associates [6] and Francis [7] for tibial lengths of girls to exceed slightly those of boys was also observed in our series of children, even though adjustments had been made on the basis of skeletal age.

The curves representing the average growth of these bones follow an essentially straight line, until the age of 13 years in girls and of 15 years in boys when growth becomes definitely slower, until it ceases altogether. The use of skeletal, instead of chronologic, ages apparently has eliminated from the curves the phenomenon of the "growth spurt," which is commonly observed during the preadolescent years. This smoothing of the growth curve may be explained on the assumption that children who exhibit an acceleration in annual increments of length also exhibit an acceleration in annual increments of maturity, as judged from the method of assay employed. Thus, when one of these measures of growth is reported in terms of the other, the rate of growth appears to become constant rather than fluctuant. This constancy was observed in the children of our series: those who matured rapidly did show larger annual increments of growth during the preadolescent years than did those who exhibited minimal skeletal development at the same chronologic ages.

COMMENT ON THE USE OF SKELETAL AGE

In order to define the stage of relative development of a given person, some criterion in addition to age is needed. In the past, standards describing the increases in size during childhood ordinarily have been based on chronologic age units only. That such norms are not necessarily identical with those which include some measure of maturational status was clearly shown by Bayley,[8] who grouped her subjects according to whether they attained a specific bone age at an early, average or late chronologic age, and by Shuttleworth,[9] who divided children into groups according to menarcheal age or the age of maximum growth.

We attempted to utilize the tool of objective assessments of bone age as a means of eliminating individual variance in rates of maturation. As

6. Stuart, H. C.; Hill, P., and Shaw, C.: The Growth of Bone, Muscle and Overlying Tissues as Revealed by Studies of Roentgenograms of the Leg Area, Monograph of the Society for Research in Child Development, 1940, vol. 5, no. 3.

7. Francis, C. C.: Growth of the Human Tibia, Am. J. Phys. Anthropol. **25:** 323-331 (Oct.-Dec.) 1939.

8. Bayley, N.: Size and Body Build of Adolescents in Relation to Rate of Skeletal Maturing, Child Development **14:**47-89 (June) 1943.

9. Shuttleworth, F. K.: Sexual Maturation and the Physical Growth of Girls Age Six to Nineteen, Monograph of the Society for Research in Child Development, 1937, vol. 2, no. 5; The Physical and Mental Growth of Girls and Boys Age Six to Nineteen in Relation to Age at Maximum Growth, ibid., 1939, vol. 4, no. 3.

mentioned previously, the age of each irregularly maturing child in our series was adjusted before the averages were computed.

The effect, as well as the importance, of such adjustments is apparent when comparison is made of the average values obtained for groups exhibiting various rates of maturation. Patterns of growth were described by Bayley, Shuttleworth and others for body measurements derived from subjects variously indexed for the rate of maturation. They observed not only that the values were remarkably different for each maturational age group at each age level, but also that the groups tended to reverse their relative positions as maturity was approached. Separate averages were computed for the boys in our series who showed accelerated, normal or retarded skeletal ages between the ages of 9 and

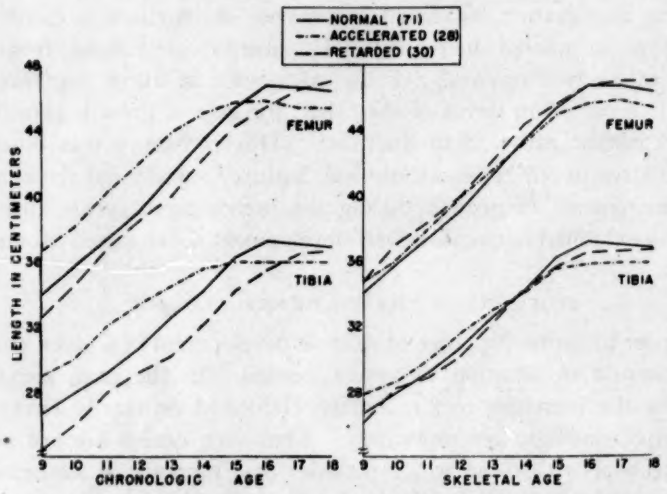

Fig. 5.—Curves of average lengths of the bones derived for three groups of boys subdivided according to rate of maturation. Left, when the averages are derived at chronologic age levels, the patterns show considerable variance. Right, the curves for the three groups become similar when the averages are computed using the skeletal age, rather than the chronologic age, of each child.

18 years (fig. 5). Each of these three groups showed a characteristic pattern of bone growth when the average values were derived according to chronologic ages; the pronounced shift in their relative positions was apparent after about 15 years of age. After each child was individually adjusted on the basis of his osseous development, however, the resultant curves for the same three groups followed comparable contours, and the tendency for the shift in relative positions at the upper age levels was considerably reduced.[10] In fact, no difference which was statistically

10. Our material would tend to indicate that a finer tool for the assessment of rates of maturity might serve to obliterate entirely the differences in patterns of growth exhibited by these three groups.

significant was found among the averages for the three groups at any skeletal age level (except in girls below the age of 9 years: these measurements were omitted from the averages reported).

The accuracy of prediction of mature dimension is considerably increased when skeletal ages are used in this way. The use of an osseous developmental index, by evaluating and adjusting the factor of variable maturation, serves to stabilize the position of the individual child in relation to the group averages. That the use of such an index also assures greater accuracy in predictions of lengths at maturity is shown in the femoral growth of 3 boys (fig. 6). The predicted adult femoral length of 2 of the boys might have been in error by as much as 4 cm., if judged from the size attained at their youngest chronologic age. The values predicted on the basis of skeletal development, however, are not

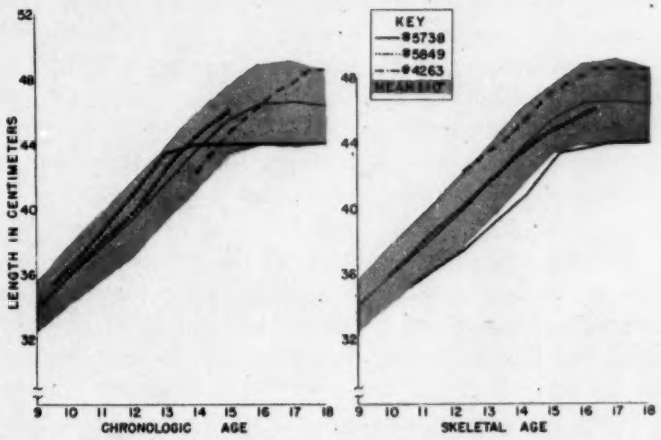

Fig. 6.—Growth curves of 3 boys with decidedly different rates of maturation. Left, when plotted according to chronologic age, the bone lengths of the 2 boys occupying the extreme positions are seen to reverse their positions in relation to the group average as they approach maturity. Right, if skeletal age is used, these same boys tend to maintain their relative positions throughout.

far different from the measurements actually observed when the boys reached the older age levels. The inclusion of such rapidly or slowly maturing children in our averages after the adjustment for skeletal age made the resultant values more stable and considerably reduced the deviation from the mean lengths during the preadolescent years when the rates of growth are commonly more irregular.

SUMMARY

Curves are presented for the lengths of the normal femur and tibia in boys and in girls from the age of 5 years until epiphysial closure. The data were derived from two groups of children who are being followed in longitudinal fashion until maturity is attained.

These averages were based on orthoroentgenographic measurements, which give true values for the lengths of the bones. Measurements included both the proximal and the distal epiphyses of each bone.

Particular attention is given the factor of variation in rates of skeletal maturation. These averages have been constructed and are to be used on the basis of skeletal age. This use of skeletal age has the effect of providing a single standard for comparing the sizes of "early-maturing, average-maturing and late-maturing" children during their growing period, without the necessity of waiting to determine the "age of maximum growth" or the age of attainment of mature skeletal age. In addition, a stabilizing factor in the estimation of adult lengths of bone is provided by using skeletal ages in the construction of norms covering the years of active growth.

300 Longwood Avenue.

USE OF CONTINUOUS CAUDAL ANALGESIA FOR CONTROL OF HYPERTENSION IN ACUTE NEPHRITIS

JAMES G. HUGHES, M.D.

GEORGE S. LOVEJOY, M.D.

HARVEY D. LYNN, M.D.

AND

ROBERT A. HINGSON, M.D.

MEMPHIS, TENN.

THE MAJORITY of children with acute nephritis have arterial hypertension, which is generally considered to be due to widespread arteriolar spasm.[1] The cause of this vasospasm may be renal ischemia, resulting in the production of excessive amounts of renin. According to this theory, the excessive amounts of renin act in the plasma on the angiotonin precursor to produce increased amounts of the active vasoconstrictor agent angiotonin, which incites the arteriolar spasm.

Excessive hypertension in persons with acute nephritis may be dangerous from two standpoints: 1. It may, possibly in conjunction with changes in the myocardial fibers, precipitate cardiac failure. 2. Severe vasospasm of cerebral vessels associated with the hypertension may produce anoxia of brain tissue and lead to the cerebral manifestations commonly called hypertensive encephalopathy. These manifestations may consist of restlessness, dimness of vision, sudden blindness, diplopia, headache, drowsiness, vomiting, and severe convulsions, resulting in death. Cerebral vasospasm, rather than cerebral edema, apparently accounts for the majority of these phenomena.[1]

In view of the hazards associated with severe hypertension in acute nephritis, it has been common practice to take active and aggressive measures to control the high blood pressure. The sheet anchor of therapy has long been magnesium sulfate, which acts by relaxing arteriolar spasm. The drug may be given orally, intramuscularly or intravenously, or in combinations of these routes. It is uncommon in our

From the Division of Pediatrics and the Division of Obstetrics and Gynecology, the University of Tennessee College of Medicine.

1. Rubin, M. I.: Acute Glomerulonephritis, in Nelson, W. E.: Mitchell-Nelson Textbook of Pediatrics, ed. 4, Philadelphia, W. B. Saunders Company, 1945, pp. 969-982.

experience, except when cardiac failure is present, for the hypertension of acute nephritis to fail to respond satisfactorily to magnesium sulfate given intramuscularly in a dosage of 0.2 cc. of a 50 per cent solution per kilogram of body weight every four to six hours, the interval depending on the response of the blood pressure. If large quantities of urine are being produced, the dose may have to be increased in order to achieve the proper effect, whereas if oliguria or anuria is present the dose must be reduced in order to avoid excessive levels and toxicity.[1] We have rarely had to resort to the intravenous administration of the drug for nephritic patients hospitalized early in the course of their disease.

Two children with acute nephritis associated with extreme hypertension and cardiac failure who failed to respond satisfactorily to administration of magnesium sulfate and other measures were recently encountered at the John Gaston Hospital, Memphis. Since continuous caudal analgesia had been used successfully in the reduction of the extreme hypertension of obstetric patients with eclampsia,[2] it was decided to employ this method in treatment of the 2 children. More recently, caudal analgesia has been used in the treatment of 2 additional patients with acute nephritis, 1 of whom was an adult. Magnesium sulfate was not used in the treatment of the last 2 patients. It is the purpose of this paper to present the case histories of these patients, to give the doses of the anesthetic agent we have found advisable for children and to discuss the probable mechanisms by which reduction in arterial hypertension is achieved. The doses recommended are derived from studies of the use of the method not only in the cases here reported, but also in others without nephritis.

As far as we have been able to ascertain, the cases to be reported are the first of children with acute nephritis for whom continuous caudal analgesia has been employed. Further studies are being made with a view to defining more clearly the indications for use of the method, to determining possible hazards involved when treating small children and to clarifying the mechanisms which operate to reduce the hypertension.

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2. (*a*) Edwards, W. B., and Hingson, R. A.: Continuous Caudal Anesthesia in Obstetrics, Am. J. Surg. **57**:459-464 (Sept.) 1942. (*b*) Siever, J. A., and Mousel, L. H.: Continuous Caudal Anesthesia in Three Hundred Unselected Obstetric Cases, J. A. M. A. **122**:424-426 (June 12) 1943. (*c*) Mylks, G. W., Jr.: Report on the Use of Continuous Caudal Anesthesia in Sixty-Five Obstetrical Cases, Canad. M. A. J. **52**:169-173 (Feb.) 1945. (*d*) Lull, C. B., and Hingson, R. A.: Control of Pain in Childbirth, ed. 2, Philadelphia, J. B. Lippincott Company, 1945, pp. 289-20. (*e*) Whitacre, F. E.: Eclamptogenic Toxemia, South. Surgeon **12**:193-201 (Sept.) 1946.

REPORT OF CASES

CASE 1.—*History.*—R. M., a 10 year old Negro girl, was admitted to the Children's Hospital Sept. 24, 1946, at 4 a. m., with the chief complaint of difficult breathing. Ten days before her admission a sore throat accompanied with low grade fever had developed. Seven days before her admission a physician examined her urine and told the mother that the child had "kidney trouble." At this time her face and neck began to swell. Three days before admission she became so dyspneic that she was unable to lie down to sleep. Two days before her entrance to the hospital the dyspnea became extreme and generalized edema developed. On the day before admission a severe cough productive of pink, frothy sputum started. The urine had been noted to be very dark, and some frequency of micturition was present. The past history and the family history were not significant.

Physical Examination.—On admission her temperature was 100 F.; the pulse rate was 124 per minute; the respiratory rate was 36 per minute, and the blood pressure was 160 systolic and 130 diastolic. The weight was 65 pounds (29.5 Kg.), some of which was due to edema. The child appeared critically ill. She was extremely dyspneic and orthopneic, and she constantly coughed up and expectorated pink, frothy sputum. The pharynx was mildly inflamed. The heart was enlarged downward and to the left, the point of maximum impulse being in the sixth interspace in the left side in the anterior axillary line. The beat was rapid and forceful; the rhythm was regular, and no murmur was noted. The aortic second sound was greater than the pulmonic second sound. Expansion of the chest was diminished, but was equal on the two sides. There was decreased resonance throughout the chest. Many moist rales were noted over both pulmonary fields anteriorly and posteriorly, being more pronounced in the bases of the lungs posteriorly. The abdomen was distended, but no fluid was detected. The liver was tender and enlarged 4 fingerbreadths below the right costal arch. The eyegrounds were considered normal.

Laboratory Findings.—On her admission, blood studies revealed a red cell count of 4,400,000 and a white cell count of 13,000, per cubic millimeter, with a moderate shift to the left in the differential count. The hemoglobin content was 10 Gm. per hundred cubic centimeters of blood.

Urinalysis showed dark urine with a 3 plus reaction for albumin, 20 to 25 erythrocytes per high power field, 1 to 2 leukocytes per high power field, no casts in the first specimen but an abundance of casts in a subsequent specimen, a specific gravity of 1.014 and a p_H of 7.

The nonprotein nitrogen level of the blood was 36 mg. per hundred cubic centimeters. The serum protein was 5.3 Gm. per hundred cubic centimeters. The Kahn test for syphilis gave a negative reaction.

Clinical Course and Treatment.—The child was placed in bed with the upper portion of the body elevated; oxygen was administered; digitalis was given, and treatment with penicillin was started in an effort to combat the pharyngitis she had on admission and to forestall the possible onset of pneumonia in the edematous lungs. Five grains (0.3 Gm.) of digitalis was given by mouth initially and 1½ grains (0.1 Gm.) every six hours for four doses. The dose of penicillin was 15,000 U. S. P. units, given intramuscularly every three hours. Morphine sulfate, 1/12 grain (5 mg.), was given subcutaneously on her admission.

Through error, no magnesium sulfate was administered until noon, eight hours after her admission, at which time the blood pressure was 160 systolic and 140 diastolic. At this time, 5 cc. of a 50 per cent solution of magnesium sulfate was given intramuscularly, and 1 ounce (30 cc.) of a 50 per cent solution of mag-

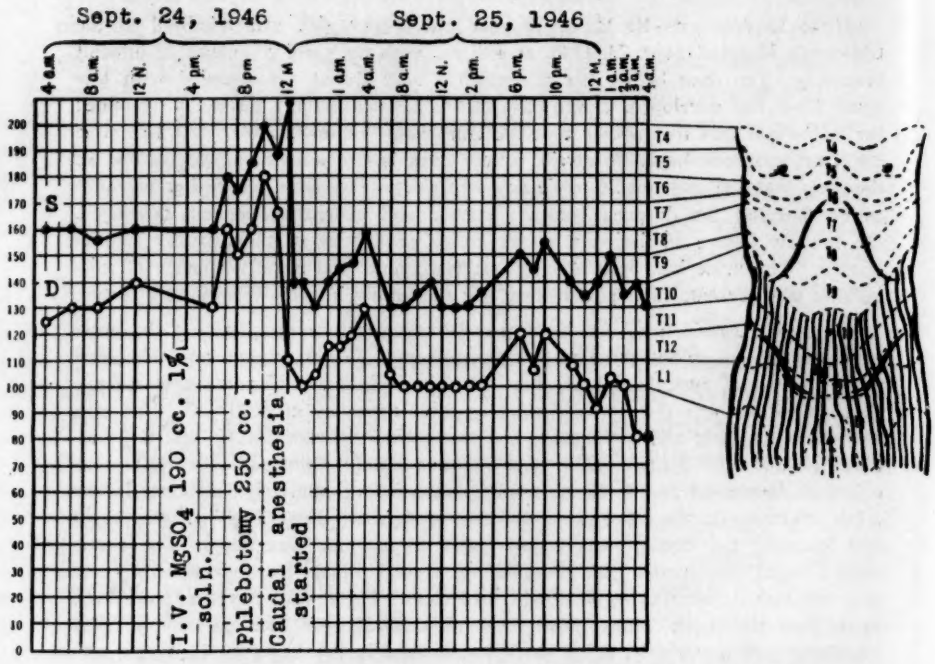

Fig. 1.—Chart showing the blood pressure recordings before and during establishment of continuous caudal analgesia and the level of anesthesia maintained in R. M. (case 1), who had acute glomerulonephritis with critical hypertension, cardiac failure, pulmonary edema and coma. Magnesium sulfate administered intramuscularly and intravenously had no effect on the hypertension, and the cardiac failure did not respond to digitalis. A phlebotomy, in which 250 cc. of blood was removed, also failed to reduce the blood pressure significantly. Caudal analgesia was started at 12:12 p. m. with 4 cc. of a 1.5 per cent solution of "metycaine hydrochloride" (see tabulation). The blood pressure immediately fell, and there was rapid return of consciousness and of cardiac compensation. The amounts of "metycaine hydrochloride," 1.5 per cent solution, which maintained continuous caudal analgesia in R. M. (case 1) for eighteen hours are here tabulated:

Date	No. of Injection	Amount, Cc.	Time
9/25/46	1	4	12:12 a.m.
	2	10	12:22
	3	15	1:20
	4	10	2:20
	5	15	3:20
	6	10	4:30
	7	15	5:30
	8	10	6:35
	9	15	8:00
	10	15	10:00
	11	15	11:30
	12	10	5.30 p.m.
Total.....		144	

nesium sulfate was administered orally. Every four hours 5 cc. of a 50 per cent solution of magnesium sulfate was given intramuscularly. The dose was increased to 8 cc. at 9:20 p. m. No response to this medication was noted. The blood pressure climbed steadily higher throughout the afternoon, being 170 systolic and 120 diastolic at 5 p. m. At this time 180 cc. of a 1 per cent solution of magnesium sulfate was given intravenously over a period of one hundred and five minutes, while the blood pressure was taken repeatedly in the arm not used for the injection. Instead of dropping, the pressure rose during the injection, so that the procedure was discontinued when 180 cc. of the solution (1.8 Gm. of magnesium sulfate) had been injected. Aminophylline, 3¼ grains (0.238 Gm.), injected intravenously gave slight relief.

So great was the pulmonary edema at 9:50 p. m. that phlebotomy was performed, 250 cc. of blood being removed. This procedure appeared to have no effect on the blood pressure, nor did it relieve the patient in the least. The pressure rose steadily until, at 11:30 p. m., it was 200 systolic and 185 diastolic and the child was in coma, extremely dyspneic, cyanotic and constantly coughing up pink, frothy sputum. There were heavy rales throughout the lungs.

As a last resort, it was decided to administer caudal analgesia (fig. 1). A 16 gage needle was inserted easily into the sacral hiatus. A ureteral catheter was passed through the needle for a distance of 6 cm. into the sacral canal by the usual technic. At 12:12 a. m., when the blood pressure was 200 systolic and 180 diastolic and the child was comatose, cyanotic and almost moribund, 4 cc. of a 1.5 per cent solution of "metycaine hydrochloride" was injected. At 12.22 a. m., ten minutes later, 10 cc. of the solution was given. At 12:27 a. m. the blood pressure had fallen precipitously to 140 systolic and 110 diastolic, and at 12:45 a. m., without a subsequent injection, it was 130 systolic and 100 diastolic. The pulse rate was 120 per minute at this time. A remarkable change now came over the patient. She awakened from her coma, conversed with the physicians, became less apprehensive, breathed more easily and two hours later dropped off into a quiet and restful slumber. There was no doubt that cardiac compensation had been swiftly and completely reestablished. Caudal analgesia was continued intermittently as necessary to control rising blood pressure for eighteen hours, after which it was discontinued. The child made an uneventful recovery (fig. 2). The urine cleared to a remarkable degree in four days, but subsequently a few red blood cells were detected daily until twenty-three days after her admission.

CASE 2.—*History and Physical Examination.*—S. T., an 11 year old Negro girl, was admitted to the Children's Hospital, March 12, 1946, because of generalized swelling and dark urine. Ten weeks prior to admission she had had an infection of the respiratory tract of unknown type, which lasted two weeks. The child did not feel well after this illness and did not return to school. Two weeks prior to her admission the urine appeared dark and smoky and a painless swelling of one side of the face developed, which disappeared in four days. One week before her admission to the hospital her eyelids, face and hands began to swell, and three days before admission the abdomen became enlarged. Two days before admission she complained of headaches and weakness.

On her admission, the temperature was 99 F., the pulse rate 100 per minute, the respiratory rate 24 per minute and the blood pressure 230 systolic and 170 diastolic. She was so critically ill on admission that she was not weighed. She was poorly nourished, appeared extremely anemic and had generalized edema of moderately severe degree. The mucous membranes were pale. There was blood-tinged saliva in the mouth. The heart was enlarged downward and to the left.

There was a systolic blowing murmur, heard best at the apex but audible over the entire precordium. Numerous rales were heard throughout the pulmonary fields, especially at the bases of the lungs. The liver was enlarged 1 finger-breadth below the right costal arch. There was evidence of the presence of fluid in the abdominal cavity.

Laboratory Findings.—On her admission blood studies revealed a red cell count of 1,570,000 per cubic millimeter, a hemoglobin content of 3.25 Gm. per hundred cubic centimeters and a white cell count of 19,350. Of the leukocytes, 91 per cent were polymorphonuclear cells, and there was a moderate shift to the left. Urinalysis revealed dark, smoky urine with a 3 plus reaction for albumin and 30 to 40

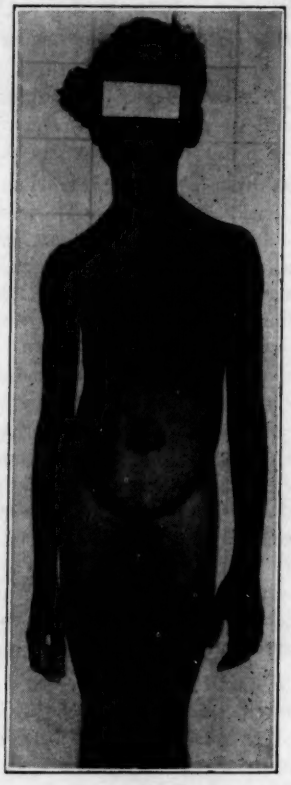

Fig. 2.—R. M. after her uneventful recovery from acute glomerulonephritis with congestive heart failure and coma.

erythrocytes and 4 to 5 leukocytes per high power field. No casts were noted on the first urinalysis, but subsequent examinations showed granular, hyaline and red blood cell casts. The specific gravity was 1.018. The p_H was 5.5. The test for glucose showed a negative reaction.

On her admission the nonprotein nitrogen value for the blood was 210 mg. per hundred cubic centimeters. The serum protein was 5.8 Gm. per hundred cubic centimeters. The carbon dioxide-combining power was 24 volumes per cent.

Clinical Course and Treatment.—The clinical course was stormy and increasingly severe. Moderate oliguria on admission progressed to almost complete anuria.

Three determinations of the nonprotein nitrogen of the blood made on the first three consecutive days showed levels of 210, 325 and 270 mg. per hundred cubic centimeters. The child was stuporous and, over a three day period, became comatose and had severe generalized convulsions. The blood pressure rose to extremely high levels, the highest being 260 systolic and 220 diastolic.

Treatment included administration of oxygen, digitalis and magnesium sulfate, blood transfusions to combat the severe anemia, use of plasma and penicillin and limitation of fluid intake orally.

Twenty-one hours after her admission to the hospital, continuous caudal analgesia was started in an effort to reduce the extreme hypertension and to allow the heart to compensate. When caudal anesthesia was started, the blood pressure was 238 systolic and 190 diastolic. Within twenty-five minutes after the procedure was started, and after a total of 13 cc. of 1.5 per cent metycaine hydrochloride had been injected, the blood pressure had fallen to 178 systolic and 126 diastolic. This initially favorable response was maintained for one hour. Then the blood pressure started to rise in spite of the continuous caudal analgesia, and the patient had a generalized convulsion. Continuous caudal analgesia was maintained for approximately thirty hours, but to no avail. The child's blood pressure surged upward on several occasions to systolic levels of 225 or higher, twice reaching 260.

In contrast to the first case presented,, in which dramatic reduction of hypertension was obtained and maintained, with correction of cardiac decompensation, a favorable response was obtained in the second case only at the start of continuous caudal analgesia. However, it is apparent that this case represented the severest type of nephritis, which causes death through cardiac failure, hypertensive encephalopathy and uremia.

Case 3.—J. C.,[3] a white man aged 25, was admitted to the Baptist Memorial Hospital on Nov. 25, 1946, with complaints of abdominal pain, fever, swelling of the face and diminution of urinary output. A diagnosis of acute nephritis and mild diabetic acidosis was made. The patient was known to have diabetes and had been receiving regulated amounts of insulin for several years. On the day after his admission to the hospital total anuria developed and persisted for four days, during which time the nonprotein nitrogen level of the blood rose from 30 to 86 mg. per hundred cubic centimeters and the blood pressure rose from 96 systolic and 72 diastolic to 160 systolic and 90 diastolic. After four days of total anuria continuous caudal analgesia was instituted, and a flow of 20 cc. of urine was collected in the first twenty minutes with an indwelling catheter. The continuous caudal analgesia was maintained for approximately seventy-two hours in an attempt to foster further excretion of urine and to control the hypertension, which reached a systolic level of 170 mm. When injections of quantities of 1.5 per cent metycaine hydrochloride sufficient to raise the level of analgesia to the sixth thoracic segment were given, the blood pressure fell promptly to levels of 110 to 120 systolic and 50 to 70 diastolic. This effect was noted eleven times in the seventy-two hours of continuous caudal analgesia and occurred with great regularity. The patient was subjectively more comfortable after each injection. However, the flow of urine was scant throughout the entire period during which caudal analgesia was maintained to the level of the sixth thoracic segment.

3. Through the courtesy of Dr. Jacob Alperin we are permitted to report this case.

Since the nonprotein nitrogen level had risen to 204 mg. per hundred cubic centimeters on the third day of continuous caudal analgesia, the patient's physician ordered a mercurial diuretic to be given intravenously. This medication was repeated the next day. A slight increase in the flow of urine was noted, and the daily output steadily increased. The nonprotein nitrogen fell to a normal level in two weeks, and the patient made an uneventful recovery. The diabetes was treated with insulin and other measures. During the period in which the increase in flow of urine was noted, the apparatus for continuous caudal analgesia was left in place for use if extreme hypertension occurred, but the blood pressure did not again become high, and no further injection of metycaine was given after the third day of caudal analgesia.

The important point to be noted in this case is the regular and repeated lowering of blood pressure associated with injections of 1.5 per cent metycaine hydrochloride, which achieved levels of caudal analgesia to the sixth thoracic segment. To what extent these repeated injections prevented hypertension from reaching greater heights cannot be known. The fact is that the arterial pressure was always under control and could be lowered regularly at will with the use of continuous caudal analgesia. It is apparent that in this case the method failed to stimulate diuresis to a satisfactory degree.

CASE 4.—*History and Physical Examination.*—C. H.,[4] a 13 year old white boy, was admitted to St. Joseph Hospital Nov. 19, 1946, with a history of a sore throat for about ten days and of headache, abdominal pain, fever and anuria for three days prior to admission. For seven days, ending two days before admission, he had received 1 Gm. of sulfadiazine every four hours, or approximately 42 Gm. of the drug. For three days prior to admission he had had almost total anuria, as well as an urticarial rash, conjunctivitis, edema of the face, faulty vision, generalized abdominal pain, nausea and vomiting. He stated that for two days before admission the only colors he could recognize were black, gray and red. His first physician had advised him to limit the intake of fluids because of vomiting. He consulted a second physician, who hospitalized him immediately.

Physical examination revealed that the patient was well developed and well nourished, but edematous and in semistupor. The pulse rate was 100 per minute; the temperature was 101 F., and the blood pressure was 140 systolic and 90 diastolic. The abdomen was slightly distended, tender and somewhat rigid. The deep reflexes were reported to be hyperactive. The rest of the physical examination showed nothing abnormal.

Urinalysis revealed a 4 plus reaction for albumin, a 4 plus reaction for blood and 20 to 30 leukocytes per high power field. The hemoglobin content was 9.6 Gm. per hundred cubic centimeters; the red cell count was 4,440,000 and the white cell count 17,450, per cubic millimeter, while the differential count showed 92 per cent polymorphonuclear leukocytes. The Kahn test for syphilis gave a negative reaction.

The initial impression was that the anuria was due to renal block with sulfonamide crystals, but cystoscopic examination, ureteral catheterizations and lavage

4. Through the courtesy of Dr. Lyman A. Kasselberg we are permitted to report this case.

of the renal pelves failed to reveal their presence. A diagnosis of acute nephritis was then made.

On November 21, after four days of total anuria, caudal analgesia was instituted in an effort to stimulate diuresis. There was an output of 30 cc. of urine in the first hour and of 320 cc. of urine in the first sixteen hours of caudal analgesia. During the three days in which caudal analgesia was maintained, the patient excreted approximately 1,000 to 1,500 cc. per twenty-four hours.

Hypertension was not much of a problem during these three days of caudal analgesia. The blood pressure, which had been 150 systolic and 90 diastolic, was brought down initially to 130 systolic and 60 diastolic and was maintained in the range of 130 to 140 systolic and 80 to 90 diastolic. Toward the end of the three day period of caudal analgesia the pressure rose twice to 180 systolic and 120 diastolic but was brought down rapidly to 130 systolic and 100 diastolic with increases in the amounts of metycaine injected.

In spite of the increase in urinary flow, the nonprotein nitrogen level of the blood, which had been 238 mg. per hundred cubic centimeters at the beginning of caudal analgesia, on November 21, and had remained at the same level the following day, rose to 336 mg. on the second day of analgesia and reached 348 mg. per hundred cubic centimeters on the third, and final, day, November 23. On November 25 it was 268 mg., and on November 27, 252 mg., per hundred cubic centimeters.

A rapidly advancing anemia developed. The hemoglobin content, which had been 9.6 Gm. per hundred cubic centimeters on November 19, fell to 5.2 Gm. on November 23. It was 4.3 Gm. per hundred cubic centimeters on November 25, 4.8 Gm. on November 27 and 1.5 Gm. on November 28. Four blood transfusions were given during this period.

After three days of caudal analgesia, the apparatus was removed, and the patient's blood pressure hovered in the range of 130 to 150 systolic and 80 to 90 diastolic.

On November 27 the blood pressure rose suddenly to 190 systolic and 90 diastolic, and the patient became dyspneic and comatose and was placed in an oxygen tent. Evidence of cardiac decompensation was present, and pulmonary edema was severe. Continuous spinal anesthesia with procaine hydrochloride was instituted, a ureteral catheter being employed according to the Touhy technic. Caudal analgesia was contraindicated at this time because of the possibility of infection on reentrance of the sacral space. Within ten minutes after the continuous spinal anesthesia was instituted, the blood pressure fell from 190 systolic and 90 diastolic to 150 systolic and 80 diastolic. The patient then regained consciousness, and the pulmonary edema improved greatly. The child was still anoxic because of the extreme anemia; his hemoglobin content was 1.5 Gm. per hundred cubic centimeters and the red cell count, 1,100,000. Over a period of two and one-half hours the blood pressure was brought down to 110 systolic and and 80 diastolic. As the intermittent doses of procaine hydrochloride were reduced, the pressure rose to 170 systolic and 100 diastolic. A larger dose was given, and the pressure dropped promptly to 140 systolic and 100 diastolic. Reduced intermittent doses were given again, and again the blood pressure began to rise. Two generalized convulsions developed ten minutes apart, when the blood pressure reached 190 systolic and 110 diastolic. Larger doses of procaine were given, and the pressure dropped quickly to 130 systolic and 60 diastolic, where it remained until the patient's death, five and a half hours after continuous spinal anesthesia was instituted. During the last hour of life dyspnea became severe.

Gross Autopsy Observations.—External Examination: The body was that of a well developed, edematous, adolescent boy, estimated to weigh 115 pounds (52.1 Kg.) and to be 5 feet 7 inches (170 cm.) in length. The secondary sex characteristics were well developed. The skin was smooth and edematous and had a pasty pallor. No superficial lymph nodes could be palpated. There was no discharge from the ears, eyes or nose. There was a hemorrhage of the right conjunctiva. The pupils were round and equal, measuring 6 mm. in diameter. The cervical lymph nodes were not enlarged, and the jaw was set in rigor mortis. The chest was symmetric and the abdomen distended. There was no deformity in or disproportion of the extremities.

Internal Examination: Peritoneal cavity: There was a medium amount of subcutaneous fat, which was extremely edematous. An estimated 250 cc. of straw-colored fluid was observed in the cavity. There was pronounced distention of both the stomach and the jejunum. Intussusception was present approximately 20 cm. from Treitz's muscle. This invagination appeared to have been agonal, since no vascular disturbance was noted.

Pleural cavities: There was 250 cc. of straw-colored fluid in the right side of the chest and 150 cc. in the left. No adhesions were noted.

Pericardial cavity: There was 100 cc. of clear fluid in this cavity but no adhesions.

Heart: The heart was enlarged and greatly dilated and weighed 460 Gm. The epicardium was smooth and pale. The myocardium was extremely pale but contained no scar or infarcts. The valves were all smooth and patent, the tricuspid measuring 12 cm. in circumference, the mitral 10 cm., the pulmonary 6 cm. and the aortic 5 cm. The coronary arteries were smooth, and no mural thrombi were observed.

Lungs: The right lung weighed 950 Gm. and the left 800 Gm. Both lungs were filled with fluid, and the lower lobes were moderately congested with blood. There was no bronchial or vascular obstruction.

Abdominal organs: The liver weighed 2,400 Gm. and was brownish red. On cut section, it was seen to be filled with blood and was edematous. The gall-bladder was thin and filled with green bile. The ducts were patent.

The spleen weighed 140 Gm. and was dark red. On cut section it held its shape well. The pancreas was pinkish yellow and presented the usual lobulations. Both the large and the small bowel contained dark blood. No point of hemorrhage and no tumor or ulcer was observed.

The adrenal glands were yellow and of about the usual size. They presented no gross hemorrhage.

Both kidneys were large and swollen and covered with tense capsules. The right kidney weighed 260 Gm. and the left 270 Gm. The capsules were stripped away with ease, leaving a grayish, mottled surface covered with reddish brown spots, which did not exceed 3 mm. in diameter. The kidney was the classic large, "flea-bitten" one of acute glomerulonephritis. On cut section, the tissue bulged and presented a similar grayish brown, mottled appearance. The glomeruli could be seen as fine granules pointing onto the surface. The pelves and ureters were not dilated. No sulfonamide crystals were seen, and no obstruction was noted.

The mucosa of the bladder showed areas of hemorrhage and edema. The wall was thick and firm. The urethra and the prostate gland were not unusual.

Aorta: The aorta was smooth and yellow. No plaques or anomalies were noted.

Brain: On opening the skull, it was seen that the meninges were edematous and the vessels extremely congested. The convolutions were flattened, and the brain tissue was firm, almost hard. The spinal cord and the brain stem were rigid. There were several bleblike areas of edema near the medulla. No gross hemorrhage or pus was noted. The brain was fixed in a solution of formaldehyde before section. After fixation, serial sections were cut; no hemorrhage was noted. The tissue was unusually firm as a result of edema.

Microscopic Examination: Heart: The myocardial fibers were of about the usual size but were widely separated by edema. No scar or infiltration was noted.

Lungs: The alveoli contained many macrophages, serum, red blood cells and a few polymorphonuclear leukocytes. There was pronounced edema of the interstitial tissue.

Liver: The cells of the hepatic cords were widely separated by edema, and the cytoplasm contained many small vacuoles. There were a few lymphocytes about the periportal areas.

Spleen: The sinusoids of the spleen were filled with blood, and the edema was a conspicuous feature.

Kidneys: The renal capsule was of about the usual thickness. The glomeruli showed extreme proliferation of Bowman's capsule to form epithelial crescents. A few glomeruli contained hyaline thrombi and an occasional polymorphonuclear leukocyte. A striking feature of these sections was the absence of red blood cells in the glomeruli. There was extensive degeneration of the proximal convoluted tubules, many of which contained blood or blood pigment. The collecting tubules were not unusual except for a tendency toward reduplication or telescoping in some areas.

Bladder: The mucosa was edematous and infiltrated with chronic inflammatory cells. There was hemorrhage into the subepithelial connective tissue in some areas.

Anatomic Diagnosis.—The primary changes were acute glomerulonephritis, oliguria, generalized anasarca, uremia and subacute cystitis.

A secondary change was the agonal intussusception. The cause of death was acute glomerulonephritis.

In this typical case of acute glomerulonephritis, the outstanding anatomic observation post mortem, both grossly and microscopically, was edema. Continuous caudal analgesia appeared to stimulate diuresis and repeatedly reduced arterial hypertension. After caudal analgesia was discontinued, spinal anesthesia also reduced hypertension. Pulmonary edema improved remarkably with the institution of spinal anesthesia when hypertension was extreme.

HISTORICAL

The evidence that continuous caudal analgesia is capable of reducing hypertension has quite naturally come chiefly from the field of obstetrics.

In September 1942, Edwards and Hingson,[2a] reported the first use of continuous caudal analgesia in obstetrics.

They recorded the case of a patient who was having eclamptic convulsions when she was admitted to the hospital and who responded remarkably to caudal analgesia. On admission, her blood pressure was 220 systolic and 110 diastolic; she talked incoherently and complained of blurred vision. When caudal analgesia

was started, at 4 a. m., the patient immediately became comfortable, her blood pressure dropped to 140 systolic and 90 diastolic and the blurred vision cleared remarkably. Her clinical condition was so improved that caudal analgesia was maintained throughout the day, during which time checks on her blood pressure made every fifteen minutes revealed that it did not at any time exceed 150 systolic. Because of the length of the labor, the interval between administrations of the serial doses of the anesthetic agent was increased. The patient delivered spontaneously a premature, but apparently healthy, boy, weighing 5 pounds (2,268 Gm.), thirteen hours after caudal anesthesia was instituted.

In June 1943, Siever and Mousel [2b] reported the use of continuous caudal analgesia in the management of 3 cases of eclampsia. One of the 3 case histories was presented in detail.

The patient's blood pressure was 190 systolic and 110 diastolic on admission, and on the day of admission blindness developed suddenly. At this time the membranes ruptured, and she began active labor. One hour later she had a convulsion and lapsed into coma. At this time the blood pressure was 200 systolic and 120 diastolic. When continuous caudal analgesia was begun, the blood pressure dropped to 130 systolic and 90 diastolic, and the patient came out of coma and was rational for the first time in four hours. The headaches and dizziness that she had complained of all day were gone, and she stated that she felt fine. The blood pressure remained less than 150 systolic and 90 diastolic throughout the course of labor; the patient was delivered of a normal child, and she had no more convulsions or coma.

In the 2 other cases of eclampsia, records of which were not given in detail, the histories were similar and the results were equally satisfactory.

In 1945, Mylks [2c] reported the case of a preeclamptic patient whose blood pressure dropped quickly from 180 systolic and 100 diastolic, at the start of continuous caudal analgesia, to 130 systolic and 85 diastolic. During the puerperium, which was uneventful, the pressure rose slightly to 150 systolic and 90 diastolic but subsided later to a normal level.

In 1945, Lull and Hingson [2d] stated that they and physicians trained by them had in the two preceding years managed 48 patients with severe preeclampsia and eclampsia. They observed that as soon as the patient's blood pressure is reduced from 50 to 100 mm. of mercury the convulsions stop and the patient requests water and liquid nourishment. They reported that they had observed the following clinical phenomena when continuous caudal analgesia was administered:

1. Maximum vasodilatation of the lower extremities, enormously increasing the capacity of the vascular bed.

2. Lowered blood pressure, which could be maintained constantly for hours.

3. Block of the vasconstricting elements to the kidney, thereby increasing the flow of urine in the potentially anuric patient.

4. Temporary denervation of the adrenal gland, with a corresponding diminution in the formation of the endocrine vasospastic substance.

They stated:

> At the present time, it appears that continuous caudal analgesia is one of the greatest advances in the management of the eclamptic, the preeclamptic, the hypertensive, and the nephritic patient.

In September 1946, Whitacre,[20] in reporting on eclamptogenic toxemia, stated that recently in selected cases there had been considerable success with the use of the procedure. He reported a remarkable response to caudal analgesia which was given on two occasions to a patient with severe eclampsia, with immediate reduction in blood pressure on both occasions. Prior to the second institution of caudal analgesia, the patient was almost anuric, she had a convulsion and her blood pressure at the start of the procedure was 185 systolic and 148 diastolic. Shortly after caudal analgesia was begun, the pressure fell to 115 systolic and 90 diastolic, and the patient excreted 400 cc. of urine. She regained consciousness and was in good condition. Whitacre was of the opinion that the continuous caudal analgesia, which had taken effect up to the level of the diaphragm, had relieved vasospasm in the renal areas, resulting in an increase in urinary output.

Russek, Southworth and Zohman [5] utilized continuous caudal analgesia as a test in the selection of hypertensive patients for sympathectomy. Continuous caudal analgesia reduced the blood pressure to normal in 42 of 60 hypertensive patients who were given this test. Eight patients showed a moderate fall in blood pressure but remained hypertensive even at relatively high levels of anesthesia. Ten patients showed slight or no response to the test.

DOSAGE AND CHOICE OF ANESTHETIC AGENT

Dosage schedules for continuous caudal analgesia in adults have been determined by many investigators, on the basis of previous experience and volumetric measurements in the peridural space of adults, both in the cadaver and in the living normal subjects. The dose of the anesthetic agent used in establishment of continuous caudal analgesia in children has never been worked out completely. Several factors should be considered in determining the correct dose: (1) the physical condition of the patient; (2) the size, weight and height of the patient; (3) the somatic level of nerve block desired; (4) the most effective

5. Russek, H. I.; Southworth, J. L., and Zohman, B. L.: Continuous Caudal Anesthesia as a Test in the Selection of Hypertensive Patients for Sympathectomy, J. A. M. A. **128**:1225 (Aug. 25) 1945; Selection of Hypertensive Patients for Sympathectomy, ibid. **130**:927-929 (April 6) 1946.

concentration and type of local anesthetic, and (5) the systolic and diastolic blood pressure of the child.

From our experience with this method in the cases reported, as well as in other cases of children for other conditions, we have observed that the test dose of the local anesthetic for a child 4 years of age or under should be 2 cc.; for an average-sized child 6 years of age, 3 cc., and a child 8 to 10 years of age, 4 cc. The supplementary doses to attain a level of nerve block with the peridural approach at about the region of the ninth thoracic dermatome should vary from 8 cc., for the small child 4 to 6 years of age, to from 10 to 15 cc., for a child from 8 to 10 years of age.

We have observed that the most efficient drug for the release of the angiospastic element of the sympathetic nervous system is a 1.5 per cent solution of "metycaine hydrochloride" (15 mg. per cubic centimeter). This dose is repeated approximately once each hour.

From our experience with the use of continuous caudal analgesia in the comatose patient, both in pediatric and in obstetric practice, we recommend the use of the indwelling ureteral catheter to protect the patient from intrasacral trauma during uncontrolled movements.

In the first case presented the patient was 10 years of age and weighed 65 pounds (29.5 Kg.), some of which was due to edema. In spite of treatment with magnesium sulfate and other measures, she presented increasing pulmonary edema, a critical hypertension associated with coma, severe dyspnea and stertorous respiration. The blood pressure was 200 systolic and 180 diastolic. The test dose selected was 4 cc. of 1.5 per cent metycaine hydrochloride. This dose was followed in ten minutes by the administration of 10 cc. The blood pressure fell quickly to 130 systolic and 100 diastolic, with a dramatic improvement in the patient's respiration and return to consciousness. It was observed that the desired level of cutaneous analgesia could be maintained to the ninth thoracic segment with hourly doses of 10 to 15 cc. of the anesthetic agent.

COMMENT

The mechanism by which continuous caudal analgesia effects reduction in hypertension appears to be the blocking of sympathetic nerves in the areas of the body involved in the anesthesia.

Three possible modes of action appear to be present:

1. Continuous caudal analgesia produces vasodilatation of the lower extremities, which greatly increases the vascular bed. It has been shown that for an adult the quantity of blood in the lower extremities during continuous caudal analgesia is approximately 700 cc. more than that present at the start of the procedure. While no studies of a similar nature have been performed with children, it is reasonable to assume

that the same mechanism holds true, and that the increase in the vascular bed may be of great significance in decreasing the load thrown on the decompensated heart. When pulmonary edema is present, this difference may be comparable to that produced by a large phlebotomy. Dilatation of the splanchnic vascular bed is probably also produced by continuous caudal analgesia.

2. A block of some, even if not all, of the sympathetic nerve fibers to the kidneys may so relieve vasospasm in the renal arterial system as to increase notably the renal blood flow, even though the systemic blood pressure falls to more normal levels. That increased renal blood flow is brought about with continuous caudal analgesia is suggested by the well known fact that there is often an increased flow of urine once the analgesia is maintained at suitable levels. If one assumes that the hypertension of acute nephritis is due to renal ischemia with an overproduction of renin and that anything leading to the relief of renal ischemia may diminish the amount of renin thrown into the circulation, a logical explanation is at hand for the reduction in blood pressure which occurs when continuous caudal analgesia is given. What is obviously needed is a detailed study of renal blood flow before and during the administration of continuous caudal analgesia in nephritic patients or in obstetric patients with eclampsia. We are planning to make such an investigation by employing renal clearance studies on nephritic patients before and during caudal analgesia.

The sympathetic nerve fibers to the kidney arise from the sixth thoracic to the third lumbar segments of the cord, inclusive.[6] It is hardly likely that all these fibers are affected when continuous caudal analgesia is maintained at the level of the tenth somatic dermatome. However, a sufficient number of the fibers may be blocked to increase considerably the blood flow to the kidneys.

3. That continuous caudal analgesia may produce a temporary denervation of the adrenal gland is the third possibility. However, the nerve supply to the adrenal gland comes through the great splanchnic nerve, which arises from the cord from as high as the fourth or fifth thoracic segment and as low as the ninth or tenth thoracic segment.[6] It does not appear, therefore, that continuous caudal analgesia would so affect the sympathetic nerves to the adrenal medulla as to produce a diminished output of epinephrine, with resultant fall in blood pressure.

It is our belief that continuous caudal analgesia reduces the hypertension associated with nephritis or eclampsia by producing a pronounced increase in blood flow to the lower extremities, and that it probably so increases the blood flow to the kidneys that renal ischemia

6. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945.

is diminished, leading to decreased production of renin and a resultant fall in blood pressure. Dilatation of the splanchnic bed is probably produced also.

From our limited experience with the use of continuous caudal analgesia in the treatment of acute nephritis, we are of the opinion that the method holds promise, particularly in the control of hypertension when cardiac failure is present or imminent, and that it may prove to have value in stimulating diuresis when oliguria or anuria is present. Since magnesium sulfate, when used in proper dosage, generally effects a rapid reduction in blood pressure, it would seem that only the exceptional patient with acute nephritis would profit from the institution of caudal analgesia.

It is apparent from the 4 cases reported here that 3 (cases 1, 2 and 4) represented severe types of acute nephritis, especially with regard to hypertension and cardiac failure. In the other case the patient did not have severe hypertension or cardiac failure, but his moderate hypertension responded regularly to caudal injections of metycaine hydrochloride.

Until the limitations and hazards of the method as applied to children are more fully known, it appears that the treatment might prove effective for the following types of nephritic patients: (1) patients whose hypertension is rising to extreme levels in spite of properly directed therapy with magnesium sulfate and other measures; (2) patients who have acute nephritis with cardiac failure and hypertension, especially those with pulmonary edema, and (3) nephritic patients with hypertensive encephalopathy.

We propose the use of caudal analgesia only as an adjunct to the already well established therapy. When the kidneys have suffered too grave an insult, it is not likely that any treatment now devised will reverse the process and save the patient. Cases 2 and 4 illustrate this point. Whether the early use of caudal analgesia in certain patients will minimize the damage to renal tissue by virtue of increasing blood supply to the kidneys remains for further investigation to reveal.

SUMMARY AND CONCLUSIONS

Continuous caudal analgesia was administered to 4 patients with acute nephritis, of whom 3 were children and 1 was an adult. The 3 children had extreme hypertension and cardiac failure and were in coma. Two of them had generalized convulsions and 2 uremia. The 2 uremic children had rapidly progressive anemia. Of the 4 patients, 2 had anuria and 1 almost complete anuria.

The first child responded in a remarkable manner with prompt reduction of severe hypertension, almost immediate recovery from coma,

reestablishment of cardiac compensation and a subsequent uneventful recovery. This patient had no oliguria or uremia.

The second child had almost complete anuria, uremia, rapidly progressive anemia, extreme hypertension, cardiac failure and generalized convulsions. She responded to continuous caudal analgesia with a prompt reduction of hypertension, but the effect could be maintained for only an hour. Thereafter, her blood pressure could not be controlled, and she subsequently died. Diuresis was not stimulated by caudal analgesia.

The third patient, a diabetic adult with acute nephritis, had total anuria, moderate uremia and moderate hypertension. The hypertension was repeatedly reduced with caudal analgesia, but the procedure seemed to bear no influence on subsequent diuresis, which may have been increased by other types of treatment given.

The fourth patient, a child, had total anuria, uremia, rapidly progressive anemia, hypertension, cardiac failure and generalized convulsions. Moderate diuresis followed immediately the institution of continuous caudal analgesia, and the blood pressure was repeatedly reduced by the method. However, the uremia became severer and the anemia extreme. The patient died.

The literature with respect to the use of continuous caudal analgesia as a means of treatment of obstetric patients with severe eclampsia is reviewed in order to show the sudden reduction in hypertension which may immediately follow the establishment of analgesia to suitable levels. We have been unable to find any prior accounts of use of the method for the treatment of acute nephritis in children.

On the basis of experience with continuous caudal analgesia with the patients in the present series, as well as with other children who did not have nephritis, a discussion is given of the anesthetic agent preferred, the test dose recommended and the dosage observed to be satisfactory.

The mechanisms with which continuous caudal analgesia effects reduction in hypertension are believed to be increased blood flow to the lower extremities, probable dilation of the splanchnic bed and increased blood flow to the kidneys, possibly with resultant diminished production of renin.

The use of continuous caudal analgesia may prove valuable for patients with severe acute nephritis who, in spite of the use of magnesium sulfate and other measures, continue to have extreme hypertension, cardiac failure or hypertensive encephalopathy.

NOTE.—The hypertension in 2 additional cases of acute nephritis with severe cardiac failure has responded to continuous caudal analgesia. These cases were seen too recently to be included in the present paper.

When caudal analgesia was given to a 6 year old girl who had advanced cardiac failure, the blood pressure, which was 135 systolic and 115 diastolic at the start of the procedure, fell to 115 systolic and 80 diastolic, and the patient came out of heart failure over a period of several hours. When caudal analgesia was given to a 17 year old boy with acute nephritis and severe cardiac decompensation, the blood pressure, which was 160 systolic and 110 diastolic at the start of the procedure, fell promptly to 120 systolic and 80 diastolic and remained there for five hours, at which time the patient died. The patient was considered to be almost moribund when the procedure was started.

20 South Dunlap Street (8).

SEMI-SELF-DEMAND FEEDING SCHEDULE FOR PREMATURELY BORN INFANTS

KURT GLASER, M.D.
CHICAGO

THE LITERATURE on the so-called self-demand schedule of infant feeding during the last years has shown an increasing trend toward allowing infants to regulate their own feeding with regard to time, amount and kind of food intake. This practice is quite in contrast with former rigid feeding schedules, which, in turn, were an understandable reaction of pediatricians against methods used in the years before their young specialty could influence infant care. It is believed that this reaction was justified in the light of developing civilization, which removed men more and more from nature's proved path and thus changed the mother's instinctive acts into those controlled by unfounded rules and superstitions of the time.

Like any new movement, this regimentation of babies proved radical in its initial stages and led to unnatural and unphysiologic conditions in the upbringing of infants. The reaction to this outgrowth of regimentation was the "self-demand schedule," [1] which, in turn, often went too far, as it deprived the young and inexperienced mother of the important guidance, support and security that are supplied by rules and regimens.

Trainham and associates,[2] in the report of their experiments in Detroit, pointed out that the cooperation of the mother is needed to make self-demand schedules effective. For this cooperation there is needed not only a willing mother with sufficient time and independence, but also a large amount of basic intelligence in the mother, father and other attendants of the child. This requirement alone makes a complete self-demand feeding schedule an impossibility in a large part of the population. On the other hand, it is not wished to return to the

From the Cook County Children's Hospital.

1. Davis, C. M.: Practical Application of Some Lessons of Self-Selection of Diet Study to Feeding of Children in Hospitals, Am. J. Dis. Child. **46**:743 (Oct.) 1933; Self-Selection of Diet Experiment: Its Significance for Feeding in Home, Ohio State M. J. **34**:862, 1938; Results of Self-Selection of Diets by Young Children, Canad. M. A. J. **41**:257, 1939.

2. Trainham, G.; Pilafian, G. J., and Kraft, R. M.: A Case History of Twins Breast Fed on a Self-Demand Regime, J. Pediat. **27**:97, 1945.

rigid schedule, which is injurious to the mental and emotional, and eventually also to the physical, well-being of children, as well as of adults.

At the clinic for premature infants of Cook County Children's Hospital, an endeavor has been made to establish a satisfactory medium between the two extremes. There we of the staff have supervised over 200 prematurely born children, of whom 118 at present have completed the observation period of eight months and have been used for this study.

These prematurely born infants came from unselected homes. However, by the nature of the hospital, the majority belonged to the poorer part of the population. There were 98 Negro, 18 white and 2 Japanese children.

In the following paragraphs, I shall briefly describe our feeding methods and then compare our results with the standards of physical growth of other authors.

The basic principle of our feeding method consisted in giving the mother a "lead" as to the timing and amounts of feedings, without restricting her in the use of her own initiative or in her innate desire to satisfy the baby's wishes.

Most babies were discharged from the ward (which was not under the jurisdiction of the clinic) when they exceeded the limit of 5 pounds (2,268 Gm.) by 1 to 3 ounces (28 to 85 Gm.). Their approximate formula at that time was 5 to 8 ounces (150 to 240 cc.) of evaporated milk, 8 to 12 ounces (240 to 360 cc.) of water and some additional carbohydrate in the form of sugar, "karo" syrup or "dextri-maltose." At this time the mother was instructed by the nurse in the preparation of the formula, in its exact division into six individual bottles and in a precise feeding schedule at four hour intervals. The mother returned with the baby to our outpatient department within the first two weeks after the baby's discharge from the hospital. At this first visit she usually demanded an increase in formula.

The instructions were now different from those given on discharge from the hospital. The total daily intake was increased liberally by the addition of milk, water and carbohydrate, but no direction as to division into individual bottles was given, nor did we mention an exact time schedule. Orange juice was added to the diet, and the regular administration of preparations of vitamins D and A was checked with the mother. Cereal was offered to the baby at 3 months of age, vegetable at 4 months, fruit at 5 months and egg yolk at 6 months, as the baby's appetite increased.

During the first months of our experience in the clinic, we noticed that our omission to instruct the mothers as to the exact amount and timing of each feeding led in most cases to the establishment of a complete self-demand feeding schedule. Most of the mothers made up the formula in the morning, following exact orders as to the total quantity of the daily formula, but filled the 6 to 8 ounce (180 to 240 cc.) nursing bottles full and offered them freely. Some babies consumed the "daily formula" before the day was over, whereupon the mother prepared a second feeding mixture within the same twenty-four hour period. Other babies were satisfied with the first amount prepared. There was also a considerable variation in the amounts consumed at the individual feedings. The result was that when the mother returned for the next check-up of the baby—usually two weeks later—the gain in weight was often out of proportion to our calculated amount of

"daily" caloric intake. On questioning, we found the aforementioned factors were an explanation of the rapid gain in weight. Since this method proved effective, it was continued as a routine in our clinic.

Only a few mothers asked specific questions as to the distribution of the formula over the day. They were instructed to give the baby more if he did not seem satisfied and to feed him earlier or later if he woke up before or overslept his feeding time. We also told them to omit the 2 a.m. bottle "as soon as the baby sleeps through." This advice was sufficient for almost all mothers who inquired for more instructions.

One group of mothers, interestingly enough, could not adjust to this schedule. It was the rather intelligent mother, overprotected during her childhood, who obtained her knowledge of child care by reading books. She seemed apparently too far removed from the natural ways of life to rely on her motherly instincts with a feeling of security in using her own initiative and judgment. She required exact orders as to amount and schedule of feeding. This type of mother also frequently requested telephone consultations to seek help for minor problems which arose between visits to the clinic.

With the exception of the last group, the supervision of this rather large number of prematurely born infants by a small staff was simple, and the spirit of the mothers was an extremely happy one. They did not feel deprived of their authority in the raising of their offspring and returned with pleasure to the clinic for check-up and advice.

Aside from the emotional and administrative advantages of this method, we have proof that the physical growth and well-being of our babies progressed in a manner similar to, or even better than, the average reported by other institutions. Our incidence of gastrointestinal disturbances (diarrhea and vomiting) was low. We attribute this fact to the individualized care of the infants and the eager and early return of the mothers to our clinic for advice, thus preventing major disturbances. Several mothers were informed about the various influences of the carbohydrates on the intestinal tract and learned to manage minor disturbances on their own initiative by adjusting the carbohydrate intake of the child.

The following section is an analysis of the growth of our children and a comparison with standards set by other investigators. For this analysis we selected the first 118 babies who attended our clinic. We excluded only those few whose obviously major malformations or severe illnesses interfered drastically with normal progress.

Tables 1 and 2 demonstrate the progress of our infants numerically, permitting exact comparison with other authors.

Only 3 babies weighed less than 1,000 Gm. They weighed 943, 908 and 681 Gm., respectively, at birth and 5,193, 4,582 and 5,902 Gm., respectively, at the age of 8 months. There were 2 babies of Japanese ancestry in our series; these belonged in the third group (weight at birth, 2,135 and 2,157 Gm., respectively). They reached a weight

of 7,136 and 7,640 Gm. and a height of 64.7 and 66.6 cm., respectively, at the age of 8 months, which is somewhat below the average for the white child and approximately equal to that for the Negro child.

In comparing our observations with those of other authors, we encountered certain difficulties because of the scarcity of available reports and because of different standards used by the various investigators. Hess and associates [4] gave many weight tables in their excellent book, but they used the corrected chronologic age. We felt, however, that the corrected chronologic age, which is computed from the infor-

TABLE 1.—*Gains in Weight of Infants on Semi-Self-Demand Feeding Schedule*

	Negro				White				Negro and White			
	No. of Infants	Average Weight, Gm.			No. of Infants	Average Weight, Gm.			No. of Infants	Average Weight, Gm.		
		Birth	6 Mo.	8 Mo.		Birth	6 Mo.	8 Mo.		Birth	6 Mo.	8 Mo.
Group 1: Weight at Birth, 1,001 to 1,500 Gm.												
Boys	1	1,483	5,959	6,895	0	.....	.....	.....	1	1,483	5,959	6,895
Girls	4	1,243	5,425	6,496	2	1,269	5,377	6,669	6	1,252	5,409	6,552
Average	5	1,291	5,532	6,575	2	1,269	5,377	6,669	7	1,285	5,488	6,601
Group 2: Weight at Birth, 1,501 to 2,000 Gm.												
Boys	28	1,806	6,369	7,492	4	1,810	6,402	7,325	32	1,806	6,373	7,446
Girls	27	1,802	6,154	7,155	4	1,927	6,649	7,406	31	1,818	6,220	7,187
Average	55	1,804	6,266	7,312	8	1,869	6,526	7,366	63	1,812	6,299	7,319
Group 3: Weight at Birth, 2,001 to 2,405* Gm.												
Boys	11	2,104	6,565	7,419	3	2,139	6,711	7,746	14	2,112	6,596	7,489
Girls	24	2,122	6,411	7,303	5	2,069	7,826	8,632	29	1,113	6,664	7,541
Average	35	2,117	6,461	7,341	8	2,095	7,408	8,299	43	2,113	6,641	7,524
General Average	— 95	— 1,892	—* 6,298	— 7,283	— 18	— 1,903	— 6,790	— 7,703	— 113	— 1,894	— 6,377	— 7,351

* Only 1 baby weighed 2,405 Gm. at birth; the next highest weight was 2,280 Gm.

mation obtained from the mother and the obstetric record, would lead to too many errors in our series, since the records of mothers delivered in other hospitals were not available and the mothers' verbal information was unreliable. Hess himself [5] stated that "the exact age of an infant is not easy to determine." Furthermore, Hess's study was based on a racial composition of about 4 white patients to 1 Negro patient, whereas in our clinic a ratio of about 5 Negro babies to 1 white baby prevailed.

3. Footnote deleted by author.

4. Hess, J. H.; Mohr, G. J., and Bartelme, P. F.: The Physical and Mental Growth of Prematurely Born Children, Chicago, University of Chicago Press, 1934.

5. Hess, J. H.: Premature and Congenitally Diseased Infants, Philadelphia, Lea & Febiger, 1922, p. 363.

Hess and associates,[4] however, made the statement that their prematurely born boys weighed less than the Woodbury [6] "normal" weights for boys until the age of 3 years. And that their prematurely born girls approximated the Woodbury measurements in weight between the ages of 9 and 12 months (table 3).

TABLE 2.—*Increase in Height of Infants on Semi-Self-Demand Feeding Schedule*

	Negro				White				Negro and White			
	No. of Infants	Average Height, Cm.			No. of Infants	Average Height, Cm.			No. of Infants	Average Height, Cm.		
		Birth	6 Mo.	8 Mo.		Birth	6 Mo.	8 Mo.		Birth	6 Mo.	8 Mo.
Group 1: Weight at Birth, 1,001 to 1,500 Gm.												
Boys	1	41.8	60.9	67.2	0	....	....	....	1	41.8	60.9	67.2
Girls	4	39.7	58.1	61.9	2	41.2	58.7	63.2	6	40.2	58.3	62.3
Average	5	40.1	58.6	62.9	2	41.2	58.7	63.2	7	40.4	58.6	63.0
Group 2: Weight at Birth, 1,501 to 2,000 Gm.												
Boys	28	42.3	61.8	64.7	4	44.8	64.1	67.1	32	42.6	62.1	65.0
Girls	27	43.3	61.0	64.9	4	43.7	62.8	65.4	31	43.3	61.3	64.9
Average	55	42.8	61.4	64.8	8	44.3	63.5	66.2	63	42.9	61.7	65.9
Group 3: Weight at Birth, 2,001 to 2,405 Gm.												
Boys	11	43.9	62.8	65.2	3	44.9	62.6	66.4	14	44.1	62.8	65.5
Girls	24	44.7	63.0	65.5	5	44.7	65.5	67.5	29	44.7	63.4	65.8
Average	35	44.4	62.9	65.4	8	44.8	64.4	67.1	43	44.5	63.2	65.7
General Average	95	43.2	61.8	64.9	18	44.1	63.4	66.3	113	43.4	62.1	65.0

TABLE 3.—*Comparison of Woodbury "Normal" Weights for Children and Weights of Children of Present Series, at Eight Months of age*

	Height, Cm.		Weight, Gm.	
	Woodbury	Glaser *	Woodbury	Glaser
White children				
Boys	69.3	66.8	8,310	7,505
Girls	67.8	65.9	7,750	7,829
Negro children				
Boys	66.7	64.9	7,799	7,437
Girls	66.0	64.9	7,237	7,169

* Data are taken from the records of babies weighing 1,001 to 2,405 Gm.

From table 3 it is clear that, as Hess stated, prematurely born boys will remain lighter than full term children for a longer period than girls. The white girls of our series exceeded the Woodbury "normal"

6. Woodbury, R. M.: Statures and Weights of Children Under Six Years of Age, Publication 87, United States Department of Labor, Children's Bureau, 1921.

weights at the age of 8 months, and the Negro girls approached the "normal" weights closely. These data show a more rapid growth than do Hess's observations.

In another book, by Hess and Lundeen,[7] a table is published in which the data are not broken down into separate columns for sex and race. Our series, as seen in table 4, compares favorably with this group, in spite of the fact that our babies were predominantly Negro.

TABLE 4.—*Comparison of Standard Weights (Hess and Lundeen) for Infants and Weights of Infants of Present Series*

	Weight at Birth, Gm.	Weight at 6 Mo., Gm.	Weight at 8 Mo., Gm.	Weight at 9 Mo., Gm.
Full term babies—Hess and Lundeen [7]	3,400	7,300	.....	8,500
Premature infants (1,500 to 2,000 Gm.)—Hess and Lundeen	1,628	5,775	.....	7,100
Premature infants (1,500 to 2,000 Gm.)—Glaser	1,812	6,299	7,319	.....
Premature infants (1,000 to 1,500 Gm.)—Hess and Lundeen	1,284	5,080	.....	6,740
Premature infants (1,000 to 1,500 Gm.)—Glaser	1,285	5,488	6,601	.....

TABLE 5.—*Comparison of Standard Weights (Camerer) for Infants and Weights of Infants of Present Series, as to Method of Feeding*

	Weight of Breast-Fed Infants, Gm.			Weight of Artificially Fed Infants, Gm.		
	Birth	6 Mo.	8 Mo.	Birth	6 Mo.	8 Mo.
Weight at Birth, 2,000 to 2,750 Gm.						
Camerer [9]	2,500	6,530	7,420	2,250	5,650	6,190
Glaser	2,113	6,641	7,524	2,113	6,641	7,524
Weight at Birth, Under 2,000 Gm.						
Camerer	1,740	5,510	6,090	1,590	4,890	5,280
Glaser	1,759	6,217	7,247	1,759	6,217	7,247

Ylppö [8] published a study of growth based on weight and length in 1919. His many charts, however, do not present figures for the first year of life.

Camerer [9] published tables in 1901 which can be compared with ours, as they show data for each month of the first year. Our tables

7. Hess, J. H., and Lundeen, E. C.: The Premature Infant: Its Medical and Nursing Care, Philadelphia, J. B. Lippincott Company, 1941, p. 19.

8. Ylppö, A.: Zur Physiologie, Klinik und zum Schicksal der Frühgeborenen: Das Wachstum der Frühgeborenen von der Geburt bis zum Schulalter, Ztschr. f. Kinderh. **24**:1 and 111, 1919.

9. Camerer, W.: Untersuchungen über Massenwachsthum und Längenwachsthum der Kinder, Jahrb. f. Kinderh. **53**:381, 1901.

compare favorably with his (table 5), although he studied children of German stock, whose weight measures—according to the Woodbury "normal" standards—ordinarily exceed the average for white and Negro children.

From the foregoing tables it becomes evident that from a statistical point of view an exact comparison of the findings of various investigators is difficult because of the different racial compositions of the groups of patients and the scarcity of available data. The tables give, however, sufficient proof that the babies observed at our clinic progress as well as, and in many cases better than, those treated by different methods at other institutions.

SUMMARY AND CONCLUSIONS

A group of prematurely born infants, reared on a semi-self-demand feeding schedule, has been observed at the Cook County Children's Hospital in the clinic for premature infants.

From a practical standpoint, this feeding method was convenient for the mothers, as well as for the clinic staff, because of its flexibility and simplicity.

This method has proved successful in affording emotional satisfaction to our mothers because of its possibility of adjustment to the individual needs of the infants as interpreted by the mother under the guidance of the clinic staff. This emotional satisfaction of the mother cannot but have a good influence on the mental growth of the child.

From a purely medical point of view, these babies have shown a progress in growth, as measured by their gain in weight and height, which compares favorably with data reported by other investigators employing different methods of feeding.

426 Briar Place (14).

CONGENITAL DIABETES INSIPIDUS RESISTANT TO TREATMENT WITH PITRESSIN

JOSEPH DANCIS, M.D.
JOHN R. BIRMINGHAM, M.D.
AND
STEPHEN H. LESLIE, M.D.
NEW YORK

THE URINARY output is normally determined to a large extent by the fluid intake. In certain pathologic states, the regulatory mechanism may be so disturbed that the urinary excretion of water becomes excessive, resulting in dehydration despite a theoretically adequate fluid intake. Excessive excretion of renal water which cannot be attributed to the presence of some abnormal substance in urine, such as sugar, nor to a diffuse renal disease, such as glomerulonephritis or pyelonephritis, has been classified clinically as diabetes insipidus. Most cases in which this condition is present are associated with a lesion in the neurohypophysis or hypothalamic areas and are attributable to a deficiency of the antidiuretic hormone produced by the posterior lobe of the pituitary gland. Two recent reports [1] have suggested that in certain cases of congenital diabetes insipidus the excessive urinary excretion may be due to an end-organ defect rather than a deficiency in hormonal control. Dehydration in infants, which may result from such excessive diuresis, is particularly likely to give rise to fever.[2]

This is a report on a patient who presented the problem of pyrexia associated with dehydration which was secondary to the excretion of abnormally large volumes of urine, in whom we had the opportunity to conduct various studies on the mechanism of the abnormal water balance.

From the Departments of Pediatrics and Medicine, New York University College of Medicine, and the Children's Medical Service, Bellevue Hospital, New York City.

1. (*a*) Waring, A. J.; Kajdi, L., and Tappan, V.: A Congenital Defect of Water Metabolism, Am. J. Dis. Child. **69**:323 (May) 1945. (*b*) Williams, R. H.: Nephrogenic Diabetes Insipidus Occurring in Males and Transmitted by Females, J. Clin. Investigation **25**:937, 1946.

2. Holt, L. E.: Inanition Fever in the Newly Born, Arch. Pediat. **12**:561, 1895. Bakwin, H.: Dehydration in New-Born, Am. J. Dis. Child. **24**:497 and 508 (Dec.) 1922.

REPORT OF A CASE

History.—L. K., a 6½ month old white girl, entered Bellevue Hospital on Sept. 27, 1945, for recurring unexplained episodes of fever. The information concerning her illness was limited to that contained in a letter from a physician. Inasmuch as the child was born out of wedlock, an incomplete family history was obtained. However, the mother was well, and no member of her family was known to suffer from symptoms similar to those of the patient.

The baby was born at term and delivery was normal and spontaneous. The mother's period of pregnancy was uneventful. A few days after birth the patient

Fig. 1.—Retrograde pyelogram done during previous hospitalization demonstrating the bizarre picture produced by extravasation of dye following injection under excessive pressure.

had a temperature of 105 F. associated with pyuria, for which she received penicillin orally. She was then admitted to another hospital for urologic study, including retrograde pyelograms (fig. 1), which were interpreted as demonstrating a large cystic dilatation on the right and a distorted left renal pelvis. The resulting diagnosis was "congenital disease of both kidneys with bilateral pyelonephrosis." These films were later reviewed in the light of subsequent developments and the unusual picture interpreted as being due to the escape of the dye from the renal pelvis with diffusion under the kidney capsules following

injection under excessive pressure. She was treated with penicillin and sulfadiazine, with a return of her temperature to normal. Following discharge from the hospital, she had recurring episodes of fever which continued until the time of admission. Her appetite had been poor and there had been only a small gain in weight since birth.

Physical Examination.—The temperature was 101.4 F. The blood pressure was 70 mm. of mercury systolic and 30 mm. diastolic. Physical examination at the time of entry revealed a pale, cheerful, white girl weighing 5 Kg. (11 pounds), of delicate build and in no apparent discomfort. Except for a slight vaginal discharge, there were no significant findings.

Laboratory Data.—The red blood cells numbered 4,250,000; the hemoglobin was 10 Gm. The white blood cell count averaged 8,000 cells per cubic millimeter, with a maximum rise to 24,000, with an average of 30 per cent polymorphonuclear cells, 64 per cent lymphocytes and 4 per cent monocytes. Urinalysis revealed urine reaction, acid; specific gravity, 1.004; no glucose or albumin. Microscopic examination revealed a few white blood cells from time to time, occasionally in clumps. Culture of the urine showed no growth in the first four specimens and in several subsequent specimens; a variety of organisms were grown on different occasions, including: B. coli, Aerobacter aerogenes, Staphylococcus albus and Enterococcus. Chemical examination of the blood revealed nonprotein nitrogen 25 mg. per hundred cubic centimeters, plasma sodium 139 milliequivalents per liter, plasma chlorides 105 milliequivalents per liter, calcium 9.2 mg. per hundred cubic centimeters, phosphorus (inorganic) 3.09 mg. per hundred cubic centimeters and alkaline phosphatase activity (Bodansky units) 4.2. The Wassermann reaction was negative. On roentgen examination the skull revealed no abnormalities and the sella turcica was normal in appearance; the long bones were normal, with two centers of ossification present in the wrist consistent with the child's age; the chest appeared normal. Retrograde pyelography on Oct. 29, 1945 outlined a normal upper urinary tract.

With freely administered fluids, the average intake approximated 2,200 cc. and the average urine output 1,400 cc. Two urea clearances corrected to a normal adult's surface area of 1.73 square meters were 67 and 85 cc. of plasma per minute; the urine flow was 0.8 cc. per minute and 1 cc. per minute respectively.[3] An intravenous phenolsulfonthalein test demonstrated 85 per cent excretion of dye in two hours. The glomerular filtration rate, the effective renal plasma flow and the tubular excretory mass were determined on Nov. 7, 1946 using mannitol and sodium p-aminohippurate (PAH).[4] Mannitol clearance corrected for surface area was 160 cc. plasma per minute (normal range 102 to 132 cc. per minute); PAH clearance or effective renal plasma flow corrected for surface area 427 cc. per minute (normal 490 to 700 cc. per minute); tubular excretory mass (TmPAH) 69.5 mg. per minute (normal 60 to 100 mg. per minute).[5]

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3. Holt, L. E., Jr.: Urea Clearance Tests: Their Limitations as Measure of Renal Function in Childhood, Am. J. Dis. Child. **44**:306 (Aug.) 1932.

4. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease, London, Oxford University Press, 1944, pp. 55 and 212.

5. Dr. Joseph West and Miss Barbara Johnston of the Physiology Department of New York University School of Medicine determined the mannitol and PAH clearances. The deviations from the normal values have been interpreted as not being significant.

Course.—The patient had an irregular febrile course with elevations of temperature to as high as 104 F. Administration of sulfadiazine and penicillin had no effect on the fever. Repeated examinations of the urine revealed minor abnormalities from time to time, as previously noted.

During November and part of December 1945 the patient had a purulent otitis media which confused the clinical picture. Following the resolution of the otitis, irregular rises in temperature persisted, and repeated examinations of the urine microscopically and by culture gave negative results. At this time it was observed that despite the child's capricious appetite and her failure to gain weight she would drink as much as 1,500 cc. of fluid daily. This was twice the amount of fluid ingestion expected of a child of her age and weight. Fluids were then

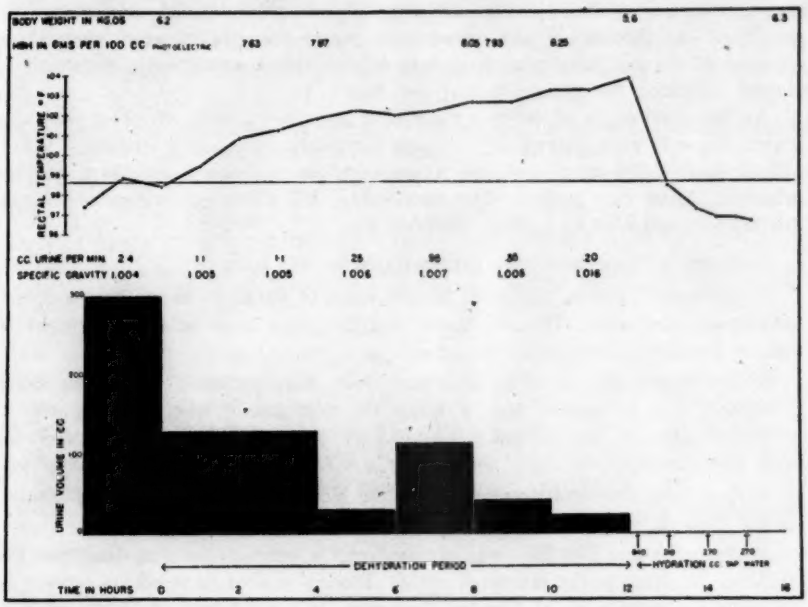

Fig. 2.—Dehydration test: Results of withholding fluid for twelve hours on the body temperature, urinary output and specific gravity, and the hemoglobin.

offered every two hours throughout the day and night. The child drank avidly, her intake rising to approximately 2,400 to 2,700 cc. daily. Her appearance and behavior improved, and her temperature for the first time since her hospitalization did not rise above normal. In fact, not uncommonly it would fall as low as 95 F., associated with profuse sweating but no evidence of discomfort. Until the present time (Dec. 15, 1946) the infant has been progressing satisfactorily. However, she is somewhat undersized, her height being 30 inches (75 cm.) and her weight 18 pounds (8.2 Kg.) at 21 months of age. Except for her excessive thirst and her small size she appears normal in all respects.

Dehydration Test.—This test was carried out in an effort to demonstrate conclusively the relationship of fever to deprivation of fluid. The patient was not given fluids for a twelve hour period. Rectal temperatures were taken every hour. The volume of the excreted urine was measured at two hour intervals. Its specific gravity was followed. Serial hemoglobin determinations were done with a

photoelectric colorimeter. The infant was weighed before and after the dehydration period. Blood for chemical examination was taken at the end of the test, and again twenty-four hours later (control examination), when the patient was in approximately her normal state of hydration as judged by her weight.

Results (fig. 2): The temperature at the beginning of the test was 98.6 F.; after twelve hours of withdrawal of fluid, 104 F. The initial weight was 13 pounds 11 ounces (6.21 Kg.); weight at the termination of the test 12 pounds 3 ounces (5.48 Kg.). The total excretion of urine for twelve hours was 750 cc. The specific gravity was 1.005 in the first specimen and 1.016 in the last specimen. Two control hemoglobin determinations before the test started were 7.9 and 7.6 Gm. per hundred cubic centimeters; after eleven hours of dehydration, 8.25 Gm. Control blood chemistry showed: nonprotein nitrogen 38 mg. per hundred cubic centimeters, total plasma protein 5.8 Gm.; plasma chlorides, 85 milliequivalents per liter. At the end of the dehydration period the results were: nonprotein nitrogen 34 mg. and total plasma protein 6.2 Gm. per hundred cubic centimeters; plasma chlorides, 86 milliequivalents per liter.

At the termination of the test the patient appeared acutely ill. Her face was drawn, the eyes were sunken, and she was extremely restless and irritable. When offered fluids 1,590 cc. of water were consumed in two hours, and there was no urination during that period. The temperature fell to normal within one hour; this was accompanied by profuse diaphoresis.

Comment.—Three facts were demonstrated by this test:

1. Excessive diuresis continued to the point of toxicity despite the complete withdrawal of fluids. The polydipsia therefore was a secondary manifestation and not the cause of the polyuria.

2. The association of dehydration and fever was confirmed. This was again illustrated in a subsequent test in which the fluid intake was restricted over a period of days to an amount approximately that which the patient received prior to the recognition of her abnormality. A low grade irregular fever resulted.

3. Results of chemical examination of the blood were not significantly altered during acute dehydration.

Pitressin Tests.—Pitressin was administered in varying doses to determine the effect of the drug on the output of urine. During a three hour period urine was collected by means of a retention catheter and measured at thirty minute intervals. In each procedure the patient was given a measured amount of fluid, sufficient to insure adequate hydration, during the twelve hours preceding the test. At the beginning of the test she was given a load dose of 250 cc. of water by mouth. The pitressin was given intramuscularly at the time the "load dose" of water was administered.

Six separate tests were performed. Two control collections determined the normal output of urine. Four tests measured the output of urine following the injection of varying doses of pitressin. The excretion of chloride was measured in some instances (table).

The urine output during the two control three hour periods was 212 cc. and 259 cc. respectively. Two pressor units were followed by excretion of 197 cc. of urine. Five pressor units which caused severe toxic symptoms resulted in a urine volume of 271 cc. With three pressor units the volume was 261 cc.; when 0.5 pressor unit was injected every half hour for seven doses beginning one-half hour before collections of urine were started, the total volume was 267 cc. The volumes of urine did not vary significantly in the individual thirty minute periods, and the specific gravity remained unchanged between 1.004 and 1.006.

There was suggestive evidence that 3 and 5 pressor units had a chloruretic effect. With these doses the excretion of sodium chloride was 141 mg. and 126 mg. respectively, while during the control periods 85 mg. and 78 mg. were excreted.

Comment.—Intramuscularly injected pitressin in graduated doses to the point of production of toxic symptoms produced no antidiuretic effect. Three pressor units administered to a 2 year old infant with apparently normal renal function produced definite antidiuresis.

Biologic Assay of Urine for Antidiuretic Substance.—These tests were based on the method of Burn [6] for estimating the antidiuretic potency of extracts of the posterior lobe of the pituitary gland.

Three tests were performed. In one, the patient was well hydrated before and during a twenty-four hour period of collection of urine. In the second she was maintained in a partially dehydrated state by limiting the fluid intake to 120 cc. every six hours for the twenty-four hour period. The degree of dehydration

The Effect of Intramuscularly Injected Pitressin on the Output, Specific Gravity and Total Sodium Chloride of the Urine

	Control			Pitressin (2 Pressor Units)			Pitressin (5 Pressor Units)		
Time in Minutes	Urine Volume, Cc.	Total Sodium Chloride, Mg.	Specific Gravity	Urine Volume, Cc.	Total Sodium Chloride, Mg.	Specific Gravity	Urine Volume, Cc.	Total Sodium Chloride, Mg.	Specific Gravity
30.....	1.5	7.70	q.n.s.	15.0	5.25	q.n.s.	37.0	18.5	1.006
60.....	45.0	8.96	1.004	20.0	5.0	q.n.s.	59.0	35.4	1.005
90.....	51.0	15.36	1.004	44.0	6.6	1.004	65.0	32.4	1.005
120.....	52.0	15.60	1.004	42.0	8.4	1.004	43.0	17.2	1.004
150.....	17.0	5.88	q.n.s.	39.0	11.7	1.004	39.0	11.7	1.003
180.....	41.0	24.60	1.004	37.0	14.8	q.n.s.	28.0	11.2	1.004
Total.....	211.5	78.10	.....	197.0	51.75	.....	271.0	126.4	.....

was reflected in the elevation of her temperature to 102 F. In the third test the patient was overhydrated by means of a continuous intravenous infusion of 3,200 cc. of 0.5 per cent of sodium chloride during a thirteen hour period. In addition the patient received 1,710 cc. of fluid by mouth during the same period. Urine was collected during the last twelve hours of the overhydration period. In this time 3,000 cc. of urine were collected, and there was a gain of weight of 0.73 Kg., with the appearance of mild edema.

Each specimen of urine was collected by placing a chemically clean glass bottle containing 15 cc. of 25 per cent acetic acid and 10 cc. of toluol beneath a special metabolism crib. The urine passed into the collecting bottle through a glass funnel containing a small quantity of glass wool which served as a filter. After completion of the collection interval, the urine was separated from the toluol in a flask; the volume, specific gravity and approximate p_H were determined. The samples were suspended in cellulose sausage casings (Visking Nojax 36/32) before the draft of an electric fan, until the volume was reduced to about 100 cc. Each specimen was dialyzed against running distilled water for five hours. Then

6. Burn, J. H.: Estimation of the Antidiuretic Potency of Pituitary (Posterior Lobe) Extracts, Quart. J. Pharm. & Pharmacol. **4**:517, 1931.

the specimens were reconcentrated to 80 cc. before the fan and finally brought to a volume of 100 cc. and a p_H of approximately 4 by the addition of distilled water and 25 per cent acetic acid.

On the morning of assay, 8 rats that had not been given food and water for a period of seventeen hours were placed in series of 4 in two metabolism cages. Each rat was hydrated with tap water to 5 per cent of its body weight and given an injection of 1 cc. of the urine concentrate intraperitoneally. Both the hydrating water and the intraperitoneal extract were administered at 37 C. Urine volumes were then measured at fifteen minute intervals until 50 per cent of the volume administered had been excreted or until three hundred minutes after onset of hydration. Similar assays of urines of 5 normal adult subjects done previously in the laboratories of the department of medicine[7] gave the following results: The averages of the number of minutes required for 25 per cent and 50 per cent excretion of total volume of water administered were 95 and 150 minutes respectively with respective time deviations of ± 12.5 and ± 24.

When duplicate assays were done on urine obtained when this patient was well hydrated, the average times required for excretions of 25 per cent and 50 per cent were 133 and 246 minutes respectively. When the patient was dehydrated, the time required for excretion of 25 per cent and 50 per cent of the urine assayed averaged 135 and 232 minutes respectively. Assay of the urine collected during the period of overhydration showed that excretion of 25 per cent required an average of 220 minutes and an excretion of 50 per cent was not reached at 300 minutes when the test was stopped. At this time only 35 per cent of the ingested water had been excreted.

All tests for the antidiuretic titer of the urine showed the presence of significant amounts of the antidiuretic substance.

COMMENT

Our original problem was to investigate the cause of the patient's unexplained fever. It is difficult to say whether or not she had pyelonephritis at the outset of her illness. However, her febrile course during the latter part of her hospitalization was amply demonstrated to be associated with and dependent on her state of hydration. The fever could be readily induced by restriction of fluids and abolished by carefully keeping the baby well hydrated.

The enormous quantities of fluid required to maintain the infant in a state of hydration suggested several approaches to the basic problem. The dehydration test demonstrated that the excessive flow of low specific gravity urine continued despite the complete restriction of fluids. This conclusively proved that the polydypsia was secondary to the polyuria. At the end of the test, at which point the patient was almost in collapse due to extreme dehydration, the specific gravity of the urine rose to 1.016. This does not exclude a primary polyuria

7. Ralli, E. P.; Robson, J. S.; Clarke, D., and Hoaglund, C. L.: Factors Influencing Ascites in Patients with Cirrhosis of the Liver, J. Clin. Investigation **24**:316, 1945.

as suggested by some,[8] for Shannon[9] has demonstrated that dogs with diabetes insipidus when dehydrated are capable of excreting a hypertonic urine.

The common diffuse renal diseases, such as chronic glomerulonephritis, pyelonephritis and polycystic kidneys, were excluded by the tests of kidney function as reported. These included mannitol and "diodrast" U.S.P. (iodopyracet compound solution) clearance studies and determination of urea clearance, phenolsulfonthalein excretion, blood nonprotein nitrogen and serum chlorides, calcium and phosphorus. Retrograde pyelography was repeated after the patient's admission to Bellevue Hospital, the upper part of the urinary tract being judged normal by this technic. Films which had been taken prior to admission and had been interpreted as demonstrating gross distention and cystic dilatation of the pelvis were reviewed by Dr. Meredith Campbell. He considered the bizarre picture as due to the escape of the dye from the renal pelvis with diffusion under the kidney capsules following injection under excessive pressure.

The neurohypophysial control of urinary output has been well demonstrated experimentally and clinically.[10] Therefore, a deficiency in this mechanism was next investigated. It appears reasonable that if the patient's excessive diuresis was dependent on a failure of production of the posterior pituitary antidiuretic factor, injection of that substance should alleviate the symptoms. Pitressin was administered intramuscularly in graduated doses to the point of toxicity without producing either urinary concentration or diminution of output. A similar dose tried on a normal infant had an antidiuretic effect.

In an attempt further to eliminate deficient function of the neurohypophysis, the urine was tested for the presence of antidiuretic substance. This was present in an amount in excess of what would be expected of a normal adult.[7] Whether or not this antidiuretic principle actually originates in the posterior lobe of the pituitary gland is a disputed question adequately covered elsewhere[11] and outside the scope of this

8. Jones, G. M.: Diabetes Insipidus: Clinical Observation in Forty-Two Cases, Arch. Int. Med. **74**:81 (Aug.) 1944. McQuarrie, I.: Water Metabolism, in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1944, vol. 7, p. 127.

9. Shannon, J. A.: Control of Renal Excretion of Water: Effect of Variations in State of Hydration on Water Excretion in Dogs with Diabetes Insipidus, J. Exper. Med. **76**:371, 1942.

10. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945, chap. 61.

11. (*a*) Ralli and others.[7] (*b*) Gilman, A., and Goodman, L.: Secretory Response of the Posterior-Pituitary to the Need for Water Conservation, J. Physiol. **90**:113, 1937. (*c*) Jones, A. M., and Schlapp, W.: Action and Fate

(Footnotes continued on next page)

paper. A review of the literature indicates that the posterior lobe of the pituitary gland elaborates an antidiuretic hormone which is excreted in the urine and the substance extracted from urine behaves in a manner similar to the antidiuretic hormone.[12]

Substantial proof that this is true has been recently offered by Pendergass and his co-workers[13] in their investigation of hypertension. Patients possessing an antidiuretic substance in their plasma were treated by irradiation of the pituitary. In the majority of cases the antidiuretic substance disappeared. Robinson and Farr have reported 3 patients with diabetes insipidus in whom no antidiuretic substance could be demonstrated in the urine.[11k] If it is accepted that the urinary substance originates in the posterior lobe of the pituitary gland then a variation in the output of the antidiuretic substance should be induced by a change in the state of hydration of the subject.[14] This did not obtain in our case, the output of antidiuretic substance remaining essentially unchanged under conditions of extreme dehydration, normal hydration and overhydration, as noted in the foregoing tests. However, it must be kept in mind that the test for the presence of urinary antidiuretic substance is actually qualitative and can be considered only roughly quantitative,[15] and that significant variations in amounts may have been induced during the tests without being detected. Further-

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of Injected Posterior Pituitary Extracts in Decapitated Cat, ibid. **87**:144, 1936. (*d*) Heller, H., and Urban, F. F.: The Fate of Antidiuretic Principle of Posterior Pituitary Extracts in Vivo and in Vitro, ibid. **85**:502, 1935. (*e*) Ingram, W. R.; Ladd, L., and Benbow, J. T.: The Excretion of Antidiuretic Substance and Its Relation to the Hypothalamico-Hypophyseal System in Cats, Am. J. Physiol. **127**:544, 1939. (*f*) Walker, A. M.: Experiments on Water Diuresis, Am. J. Physiol. **123**:210, 1938; Experiments upon the Relation Between the Pituitary Gland and Water Diuresis, ibid. **127**:519, 1939. (*g*) Arnold, O.: Ueber blutdrucksteigernde und diuresehemmende Substanzen im Harn, Arch. f. exper. Path. u. Pharmakol. **190**:360, 1938. (*h*) Hare: Personal communication to the authors; cited by Robinson and Farr.[11k] (*i*) Ham, G. C., and Landis, E. M.: A Comparison of Pituitrin with the Antidiuretic Substance Found in Human Urine and Placenta, J. Clin. Investigation **21**:455, 1942. (*j*) Dicker, S. E., and Heller, H.: The Renal Action of Posterior Pituitary Extract and Its Fractions as Analysed by Clearance Experiments on Rats, J. Physiol. **104**:353, 1946. (*k*) Robinson, F. H., and Farr, L. E.: The Relation Between Clinical Edema and the Excretion of an Antidiuretic Substance in the Urine, Ann. Int. Med. **14**:42, 1940.

12. Ralli and others.[7] Gilman and Goodman.[11b] Jones and Schlapp.[11c] Heller and Urban.[11d] Hare.[11h]

13. Pendergass, E. P., and others: The Indication for Irradiation of the Pituitary in Patients with Arterial Hypertension, Am. J. M. Sc. **213**:192, 1947.

14. Gilman and Goodman.[11b] Pickford, M.: Control of the Secretion of the Antidiuretic Hormone from the Pars Nervosa of the Pituitary Gland, Physiol. Rev. **25**:573, 1945.

15. Heller and Urban.[11d] Ham and Landis.[11i]

more, other factors difficult to control besides variations in hydration influence the output of antidiuretic hormone by the posterior lobe of the pituitary gland.[16]

Attention was next directed to the adrenal cortex, which is known to elaborate hormones that are essential to the normal control of water as well as mineral and carbohydrate metabolism.[17] A diabetes-insipidus-like syndrome has been produced in animals by the administration of desoxycorticosterone acetate [18] and the antagonistic action of the adrenal cortex extract and pitressin on the excretion of sodium, chloride and water has been confirmed in a human subject with diabetes insipidus. It is postulated that the polydypsia and polyuria associated with the administration of cortical hormones is probably related to a consistent elevation of serum sodium [19] and that the polyuria is secondary to polydipsia.[18b] The salt content of the diet plays an important role, for withdrawing salt relieved both polydypsia and polyuria.[18c] Ragan and his associates [18b] state that the diabetes-insipidus-like picture induced in dogs by desoxycorticosterone differs from pitressin-deficient diabetes insipidus in two important aspects: (1) Pitressin is relatively ineffective, and (2) restriction of fluid did not cause dehydration. Although pitressin was ineffective in producing antidiuresis in our patient, restriction of fluid rapidly produced marked dehydration. Furthermore, we have no evidence of an abnormal retention of sodium and chloride. The sodium and chloride levels were normal with the child well hydrated, and even under the stress of the dehydration test the chloride level remained unchanged. The sodium in the latter test was not determined

16. Theobald, G. W., and Verney, E. B.: The Inhibition of Water Diuresis by Afferent Nerve Stimuli After Complete Denervation of the Kidney, J. Physiol. **83**:341, 1935.

17. (*a*) Baumann, E. J., and Kurland, S.: Changes in the Inorganic Constituents of Blood in Suprarenalectomized Cats and Rabbits, J. Biol. Chem. **71**:281, 1927. (*b*) Loeb, R. F.; Atchley, D. W.; Benedict, E. M., and Leland, J.: Electrolyte Balance Studied in Adrenalectomized Dogs, with Particular Reference to the Excretion of Sodium, J. Exper. Med. **57**:775, 1933. (*c*) Hartman, A.: Functions of the Adrenal Cortex, Endocrinology **30**:861, 1942. (*d*) Harrop, G.: Influence of the Adrenal Cortex on the Distribution of Body Water, Bull. Johns Hopkins Hosp. **59**:11, 1936.

18. (*a*) Corey, E. L.; Silvette, H., and Britton, S. W.: Hypophyseal and Adrenal Influence on Renal Function in the Rat, Am. J. Physiol. **125**:644, 1939. (*b*) Ragan, C.; Ferrebee, C. E.; Atchley, D. W., and Loeb, R. F.: Polydypsia and Polyuria Induced in the Normal Animal by Desoxycorticosterone, ibid. **131**: 73, 1940. (*c*) Mulinos, M. G.; Spingarn, C. L., and Lojkin, M. E.: Diabetes-Insipidus-Like Condition Produced by Small Injections of Desoxycorticosterone Acetate in Dogs, ibid. **135**:102, 1941.

19. Anderson, J. A., and Murlin, W. R.: Antagonism of Pitressin and Adrenal Cortical Extract in Human Diabetes Insipidus, J. Pediat. **21**:326, 1942.

but in adrenal disturbances it tends to parallel the chloride level.[20] Abnormal adrenal activity would thus be fairly well excluded as the cause of polyuria in this case.

Warkany [21] mentions the possible relationship of the disease to activity of the thyroid gland. In animals with diabetes insipidus, thyroid extract greatly augments diuresis. Mahoney and Sheehan [22] reported the return of fluid intake and urine output to normal when thyroidectomy was performed on animals with diabetes insipidus originating in the posterior lobe of the pituitary gland. However, in dogs with an intact pituitary stalk, administration of thyroid has only a mild diuretic action in no way comparable to the extreme polyuria induced after occlusion of the stalk. Thus, experimentally, the thyroid does not appear to be a primary factor in polyuria. With no other evidence for thyroid disease in our patient, it does not deserve serious consideration. The possibilities left to us then are a deficiency in regulatory factors as yet unrecognized, or a primary defect in the kidney. Some work has been done [23] to indicate the presence of a diuretic factor produced by the anterior lobe of the pituitary. That there is such a hormone has not been completely accepted, and its relation to clinical disease remains to be verified.

In the absence of any evidence that the endocrine system is responsible for the patient's polyuria, the possibility of an "end-organ" defect, i. e., a lack of response of the kidneys to normal hormonal stimulation, must be considered. Waring and his associates [18a] have reported on two families demonstrating almost identical symptomatology—extreme pitressin-resistant polyuria with recurrent bouts of dehydration and fever. In their cases, serum sodium and chloride were greatly elevated during dehydration, a condition which was not present in ours. However, it is likely that the underlying mechanism of the polyuria was the same, the electrolyte variation being a secondary feature of minor importance, such as has been demonstrated in dogs with diabetes

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20. Loeb and others.[17b] Harrop.[17d] Clinton, M., Jr.; Thorn, G. W.; Eisenberg, H., and Stein, K. E. Effect of Synthetic Desoxycorticosterone Therapy on Plasma Volume and Electrolyte Balance in Normal Dogs, Endocrinology **31**:578, 1942.

21. Warkany, J., and Mitchell, A. G.: Diabetes Insipidus in Children: Critical Review of Etiology, Diagnosis and Treatment with Report of Four Cases, Am. J. Dis. Child. **57**:603 (March) 1939.

22. Mahoney, W., and Sheehan, D.: The Effect of Total Thyroidectomy upon Experimental Diabetes Insipidus in Dogs, Am. J. Physiol. **112**:250, 1935.

23. Best and Taylor.[10] Richter, C. P.: Experimental Diabetes Insipidus in Relation to the Anterior and Posterior Lobes of the Pituitary, Am. J. Physiol. **110**:124, 1934.

insipidus [24] and in other cases of dehydration due to loss of fluid.[25] It was Waring's conclusion that the primary defect was in the renal tubules with diminished reabsorption of water.

Williams [1b] came to a similar conclusion in his report on 7 members of one family. Three of the patients were demonstrated to be "pituitrin"-resistant. Renal clearance studies with mannitol, "diodrast" and creatinine done on 1 patient indicated impairment of tubular function, while 4 more of the patients are said to have had varying degrees of impairment of kidney function, the details of which are not given.

Many interesting comparisons can be drawn between these patients and infants of the newborn period. Both show the production of urine of low specific gravity, resistance to pitressin [26] and a tendency toward dehydration with associated fever. The reason that dehydration and dehydration fever are not a constant feature of the newborn period is that the glomerular filtration rate is also low at this time and the total urine volume corresponds well with adult values as corrected to surface area.[27] Probably during maturation of the individual increases in tubular reabsorption and pitressin sensitivity keep pace with increases in glomerular filtration rate maintaining the infant in a balanced state of hydration. This maturation process probably depends on the development of an enzyme system on which the antidiuretic hormone has an effect.[28] When, however, the tubular reabsorption lags, dehydration supervenes. This ordinarily is a transient complication of the newborn period. In our patient, however, a deficiency in the maturation of tubular function may have persisted and may represent the mechanism for the production of her symptoms.

SUMMARY

The case of an infant is reported in whom the presenting problem of recurrent bouts of unexplained fever was demonstrated to be secondary to dehydration resulting from extreme polyuria.

24. Hare, R. S.; Hare, K., and Philips, D. M.: The Renal Excretion of Chloride by the Normal and by the Diabetes Insipidus Dog, Am. J. Physiol. **140**: 343, 1943.

25. Hamilton, B.; Kajdi, L., and Meeker, D.: The Acidosis of Acute Diarrhea in Infancy, Am. J. Dis. Child. **38**:314 (Aug.) 1929.

26. Heller, H.: The Renal Function of Newborn Infants, J. Physiol. **102**:429, 1944.

27. McCance, R. A., and Young, W. F.: The Secretion of Urine by Newborn Infants, J. Physiol. **99**:265, 1941.

28. Cutting, M., and McCance, R. A.: The Metabolism of Kidney Slices from New Born and Full-Grown Rats, J. Physiol. **104**:288, 1946.

It is believed that the polyuria is not due to deficiency in neurohypophysial activity, because (1) the polyuria did not respond to the administration of pitressin and (2) an antidiuretic substance presumably derived from the pituitary was present in the patient's urine in large amounts.

Other possible mechanisms for the production of polyuria are discussed. It is suggested that in this patient the excessive diuresis may be due to a congenital anomaly of kidney function resulting in a kidney unable to respond to normal hormonal control.

INDIVIDUAL DIFFERENCES IN PHYSICAL CHANGES ASSOCIATED WITH ADOLESCENCE IN GIRLS

EARLE L. REYNOLDS, Ph.D.
AND
JANET V. WINES, A.B.
YELLOW SPRINGS, OHIO

THE PEDIATRICIAN, in serving his adolescent patients, can profitably employ a knowledge of the individual differences which exist in the processes of sexual maturation.[1] A recent editorial in *The Journal of the American Medical Association* emphasized this fact, concluding, "The pediatrician is in a strategic position to aid developing adolescents in understanding and evaluating their own development."[2]

It is certainly true that many of the psychologic tensions and inadequacies of the adolescent have a physical or physiologic basis, related to differentials which often exist in body size, sexual maturation and social or intellectual maturity.

> There are widely accepted behavior expectations for children of differing degrees of physical maturity. . . . The body parts and characteristics and functional properties do not mature evenly. . . . The appearance of the adolescent sometimes will not be in harmony with his physiological maturity; a mature appearing adolescent may have a child's tolerance for tobacco or alcohol, or a childish resistance to fatigue.[3]

There is little doubt that, in the study of the growth, development and behavior of adolescents, individual differences in sexual maturation play an important role.[4]

From the Fels Research Institute for the Study of Human Development, Antioch College.

1. Symposium on Adolescence, J. Pediat. **19**:289-402 (Sept.) 1941.

2. Physiologic Standards in Adolescence, editorial, J.A.M.A. **132**:863 (Dec. 7) 1946.

3. Barker, R. G.; Wright, B. A., and Gonick, M. R.: Adjustment to Physical Handicap and Illness, Bulletin 55, Social Science Research Council, New York, 1946, chap. 2, pp. 8-54.

4. (*a*) Washburn, A. H.: The Significance of Individual Variations, J. Pediat. **8**:31-37 (Jan.) 1936. (*b*) Jones, H. E.: The Adolescent Growth Study, J. Consult. Psychol. **3**:157-159 and 177-180, 1939. (*c*) Frank, L. K.: General Considerations: Certain Problems of Puberty and Adolescence, J. Pediat. **19**:294-301 (Sept.) 1941. (*d*) Jung, F. T.: The Physiological Changes Incident to

(Footnote continued on next page)

Jung [4d] pointed out that knowledge of simple numerical facts about puberty helps to provide the data on which diagnosis and treatment of abnormalities may be based. The purpose of the present paper is to examine various types of individual variations in female sexual maturation, particularly the shape, size and maturation of the breasts, the development of pubic hair, the advent of the menarche and certain aspects of body size and shape. Data obtained from 557 semiannual examinations of 49 girls at the Fels Research Institute provided the materials for analysis.[5]

The general order of appearance was determined for the various external physical changes accompanying pubescence in girls. The maturational sequence, as described by Priesel and Wagner [6] and confirmed by Pryor [7] and others, includes rounding of the hips, beginning development of the breasts, appearance of pubic hair and appearance of axillary hair. The menarche usually occurs just before the appearance of axillary hair.[8] A number of general discussions of these processes have appeared recently.[9] Seckel [9f] presented in tabular form the average approximate age and sequence of appearance of normal sexual characters in both sexes, as obtained from the literature.

Puberty, Illinois M. J. **80**:477-484 (Dec.) 1941. (*e*) Greulich, W. W.; Dorfman, R. I., and others: Somatic and Endocrine Studies of Puberal and Adolescent Boys, Monograph of the Society for Research in Child Development, 1942, vol. 7, no. 3. (*f*) Stolz, H. R., and Stolz, L. M.: Adolescent Problems Related to Somatic Variations, in Henry, N. B.: Forty-Third Yearbook, National Society for the Study of Education, University of Chicago, 1944, pt. 1.

5. Sontag, L. W.: The Fels Research Institute for the Study of Human Development, Antioch College, Yellow Springs, Ohio, 1946; Biological and Medical Studies at the Samuel S. Fels Research Institute, Child Development **17**: 81-84 (March-June) 1946.

6. Priesel, R., and Wagner, R.: Gesetzmässigkeiten im Auftreten der extragenitalen sekundären Geschlechtsmerkmale bei Mädchen, Ztschr. f. menschl. Vererb.- u. Konstitutionslehre **15**:333-352, 1931.

7. Pryor, H. B.: Certain Physical and Physiological Aspects of Adolescent Development, J. Pediat. **8**:52-62 (Jan.) 1936.

8. Greulich, W. W., and Thomas, H.: The Growth and Development of the Pelvis of Individual Girls Before, During, and After Puberty, Yale J. Biol. & Med. **17**:91-98 (Oct.) 1944.

9. (*a*) Shuttleworth, F. K.: The Adolescent Period: A Graphic and Pictorial Atlas, Monograph of the Society for Research in Child Development, 1938, vol. 3, no. 3. (*b*) Meredith, H. V.: Bodily Changes in Adolescence, Hygeia **16**: 832-834 (Sept.); 927-929 (Oct.); 944-945 (Nov.) 1938. (*c*) Novak, E.: Gynecologic Problems in Adolescence, J. A. M. A. **117**:1950-1953 (Dec. 6) 1941. (*d*) Greulich, W. W.: Some Observations on the Growth and Development of Adolescent Children, J. Pediat. **19**:302-314 (Sept.) 1941. (*e*) Stuart, H. C.: Normal Growth and Development During Adolescence, New England J. Med. **234**:666-672 (May 16); 693-700 (May 23); 732-738 (May 30) 1946. (*f*) Seckel, H. P. G.: Precocious Sexual Development in Children, M. Clin. North America **30**:183-209, 1946.

Greulich [9d] may be cited as giving the usual relations:

> During normal puberty, the development of the breasts is among the earliest external manifestations of beginning sexual maturation, and the breast changes are usually well under way before the pubic hair appears in any considerable quantity. The growth of axillary hair usually begins after the pubic hair is fairly well developed and is ordinarily preceded by the menarche, the first menstruation.

In many of the studies mentioned, reference was made to the wide individual differences which exist in the processes of sexual maturation. The menarche, for instance, is commonly considered to occur within a normal age range of 9 to 17 years. It may occur even earlier, accompanied with other sexual characters, in the so-called constitutional type of female precocious puberty, with no demonstrable endocrinopathic symptoms.[10] Within much narrower limits, there are many differences between early maturing and late maturing girls, for example, in growth patterns, skeletal development, terminal size and tissue distribution.[11] Differences among girls in sexual maturation taken as a whole constitute the commonest type of variability studied.

There are, however, other aspects of differences in sexual maturation which appear to be well worth considering. One of these relates to reversals and unconformities in the developmental patterns of individual girls. Thus, there are girls who do not follow the usual sequence, in which appearance of breasts precedes appearance of pubic hair, but

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10. Novak, E.: The Constitutional Type of Female Precocious Puberty with a Report of Nine Cases, Am. J. Obst. & Gynec. **47**:20-42 (Jan.) 1944.

11. (*a*) Boas, F.: Studies in Growth, Human Biol. **4**:307-350 (Sept.) 1932. (*b*) Flory, C. D.: Predicting Puberty, Child Development **6**:1-6 (March) 1935. (*c*) Richey, H. G.: The Relation of Accelerated, Normal and Retarded Puberty to the Height and Weight of School Children, Monograph of the Society for Research in Child Development, 1937, vol. 2, no. 1. (*d*) Stone, C. P., and Barker, R. G.: On Relationship between Menarcheal Age and Certain Measurements of Physique in Girls of ages Nine to Sixteen Years, Human Biol. **9**:1-28 (Feb.) 1937. (*e*) Shuttleworth, F. K.: Sexual Maturation and the Physical Growth of Girls Age Six to Nineteen, Monograph Society Research Child Development, 1937, vol. 2, no. 5; (*f*) Sexual Maturation and the Skeletal Growth of Girls Age Six to Nineteen, ibid., 1938, vol. 3, no. 5; (*g*) The Physical and Mental Growth of Girls and Boys Age Six to Nineteen in Relation to Age at Maximum Growth, ibid., 1939, vol. 4, no. 3. (*h*) Pryor, H. B., and Carter, H. D.: Phases of Adolescent Development in Girls, California & West. Med. **48**:89-94 (Feb.) 1938. (*i*) Simmons, K., and Greulich, W. W.: Menarcheal Age and the Height, Weight, and Skeletal Age of Girls Age Seven to Seventeen Years, J. Pediat. **22**:518-548 (May) 1943. (*j*) Bayley, N.: Skeletal Maturing in Adolescence as a Basis for Determining Percentage of Completed Growth, Child Development **14**:1-46 (March) 1943; (*k*) Size and Body Build of Adolescents in Relation to Rate of Skeletal Maturing, ibid. **14**:47-89 (June) 1943. (*l*) Reynolds, E. L.: Sexual Maturation and the Growth of Fat, Muscle and Bone in Girls, ibid. **17**:121-144 (Sept.) 1946; (*m*) Differential Tissue Growth and Sexual Maturity, Am. J. Phys. Anthropol. **4**:256-257 (June) 1946.

in whom the process is reversed, so that pubic hair appears several years before the first visible signs of breast development. There are girls who at menarche show a physical development considerably less mature than that usually seen at this stage of sexual maturation, while other girls possess a mature body configuration some time before menarche occurs.

Another type of individual difference is seen in the appearance of specific sexual structures, such as pattern of distribution of pubic hair, the shape and size of the breasts and the degree of prominence of the areolar area. For example, Stratz's [12] four stage classification of breast development, involving as one stage a temporary uplift of the papilla and areola as a separate mound above the general contour of the breast, does not seem to represent a universal phenomenon of female pubescence.

Consideration will be given in the following sections to these and other aspects of variability in female sexual maturation.

MATERIAL AND METHODS

The 49 girls reported on in this paper are regular participants in the long term study of growth and development conducted by the Fels Research Institute.[5] Each of these girls has been followed since birth or early childhood, and the present report considers records beginning at the age of 8 years, a total of 557 observations. The average age of these girls is about 14, the oldest being 18, and 32 girls have reached menarche. Examinations are made at the birthday and the half-birthday and include medical examinations, menstrual record, photographs in the nude, body measurements, roentgenograms and the recording of the development of various sexual characteristics.

The distribution of the girls, by number of consecutive semiannual examinations, beginning at the age of 8, is shown in the following tabulation:

Number of examinations.	6	7	8	9	10	11	12	13	14	15	16	17	18	Total
Number of girls	2	7	7	2	2	4	7	3	4	2	5	3	1	49
Total.....	12	49	56	18	20	44	84	39	56	30	80	51	18	557

In order partially to objectify observations of pubescence, pictorial cues were used to record various stages of breast development and growth of pubic hair. These cues were obtained from an analysis of our own material and from the literature. For breast development (fig. 1), the stages distinguished by Stratz,[12] and described by Greulich and associates [13] and Pryor,[7] were used, with the inclusion of an additional (stage 3) category: (1) the infantile form: elevation of papilla only; (2) the bud stage: elevation of breast and papilla as a small mound; (3) intermediate stage: elevation of breast and areola with no distinct separation of their contours; (4) primary mamma stage; areola and papilla form

12. Stratz, C. H.: Der Körper des Kindes und seine Pflege, ed. 3, Stuttgart, Ferdinand Enke, 1909.

13. Greulich, W. W., and others: A Handbook of Methods for the Study of Adolescent Children, Monograph of the Society for Research in Child Development, 1938, vol. 3, no. 2.

a secondary mound above the level of the breast; (5) mature stage: the papilla only projects, owing to the recession of the areola to the general contour of the breast.

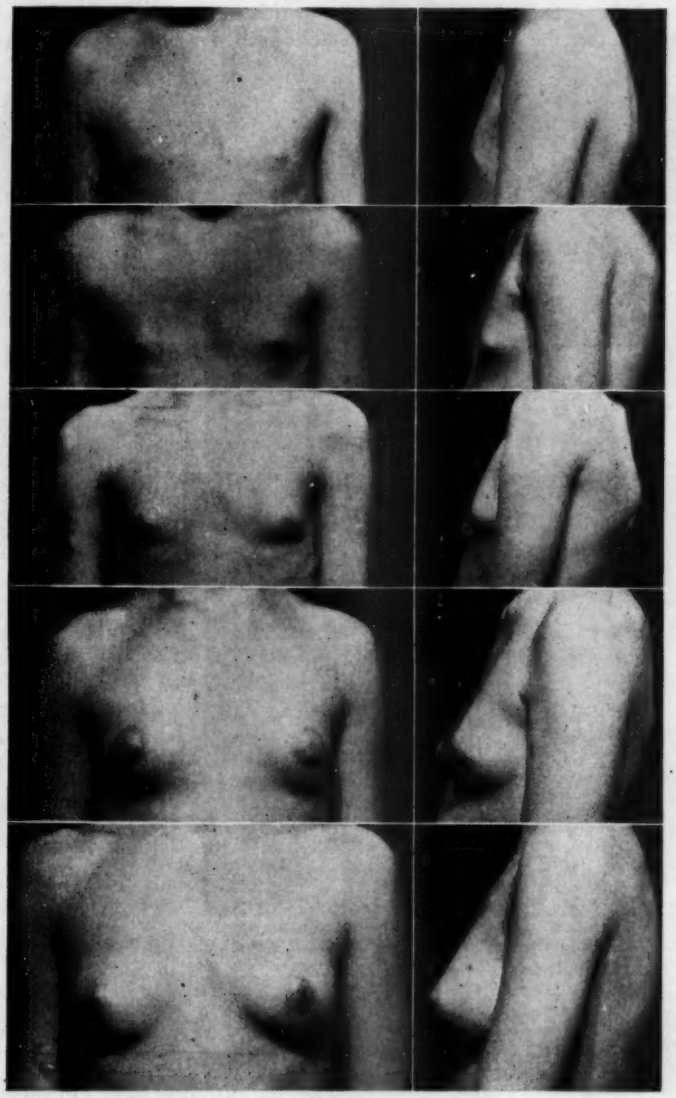

Fig. 1.—Standards for the stages of breast maturation. The pairs of photographs show, from top to bottom, the infantile, bud, intermediate, primary mamma and mature stages.

The size of the breast was classified as small, medium or large (fig. 2), and the shape of the breast as conical, hemispherical or flat (fig. 3). These characters will be described further in the next section of the paper.

Ratings of development of pubic hair were also made on a five point scale (fig. 4): (1) infantile, no pigmented pubic hair; (2) hair pigmented, straight or only slightly curled, sparse, primarily along the labia; (3) hair curled, slight spread on mons; (4) hair curled, moderate amount and spread; (5) hair tightly curled, profuse definite inverse triangular pattern extending to inguinal region, corresponding to the horizontal type described by Dupertuis and associates.[14]

RESULTS

Relations of First Appearance of Breasts, First Appearance of Pubic Hair and Menarche.—Figure 5 shows the percentage distribution of age at first breast development and first appearance of pubic hair in

Fig. 2.—Standards for breast size. These 3 girls are all in the same stage of breast maturation.

the 49 girls of the present series, and also the age at menarche of 32 girls. The mean age at bud stage of breast development was 10.8 plus or minus 1.1 years, while the mean age for first appearance of pubic hair was 11.0 plus or minus 1.1 year. Breast development began before the appearance of pubic hair in 26 girls by the following age intervals: 0.5 year, 11 girls; 1 year, 11 girls; 1.5 year, 3 girls; 2 years,

14. Dupertuis, C. W.; Atkinson, W. B., and Elftman, H.: Sex Differences in Pubic Hair Distribution, Human Biol. **17**:137-142 (May) 1945.

1 girl. Pubic hair appeared before the beginning of breast development in 16 girls at the following age intervals: 0.5 year, 7 girls; 1 year, 4 girls; 1.5 year, 2 girls; 2 years, 1 girl; 2.5 years, 1 girl; 3.5 years, 1 girl. In 7 girls, the two characteristics appeared at approximately the same age. Breast development thus appeared a

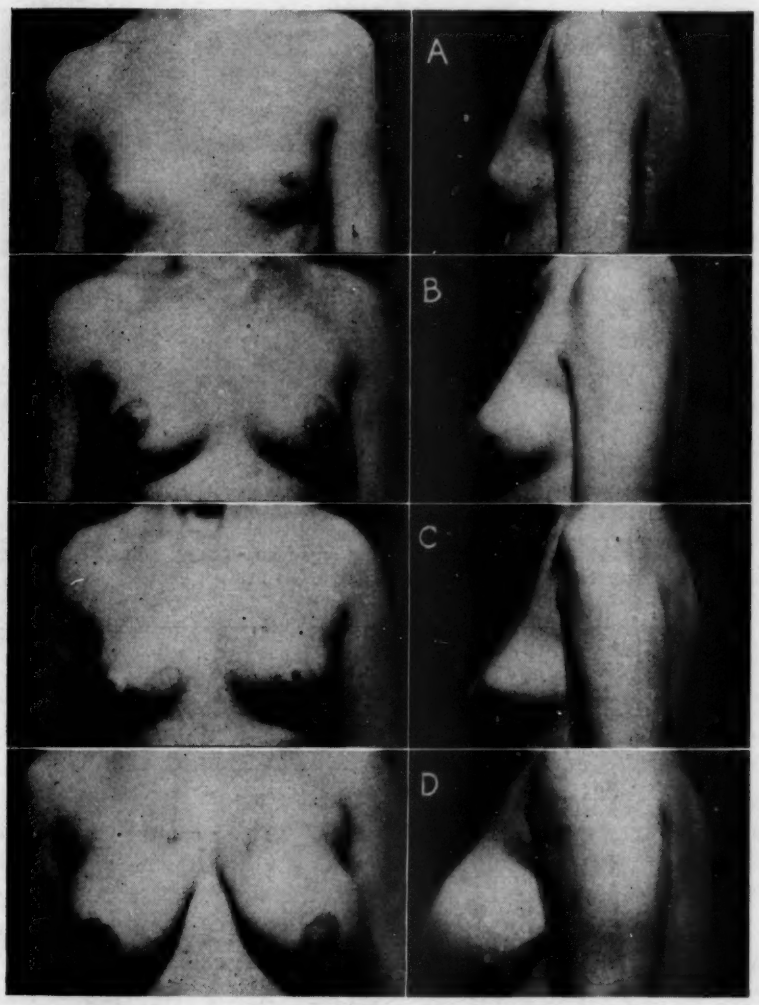

Fig. 3.—Standards for breast shape. Pair *A* shows the flat type; *B*, the hemispherical type; *C*, the conical type, and *D*, a distorted type due to obesity. These 4 girls are all at menarche.

year or more before pubic hair in 15 girls, while pubic hair appeared a year or more before the beginning of breast development in 9 girls.

The mean age at menarche was 12.9 ± 1.4 years. As judged by the coefficient of correlation (r), age at menarche appears to be more

closely associated with appearance of breasts than with appearance of pubic hair: The r between age at menarche and age at appearance of breast buds was +0.86, while the r between age at menarche and first appearance of pubic hair was +0.70. The r between age at appearance of breast buds and age at appearance of pubic hair was +0.66.

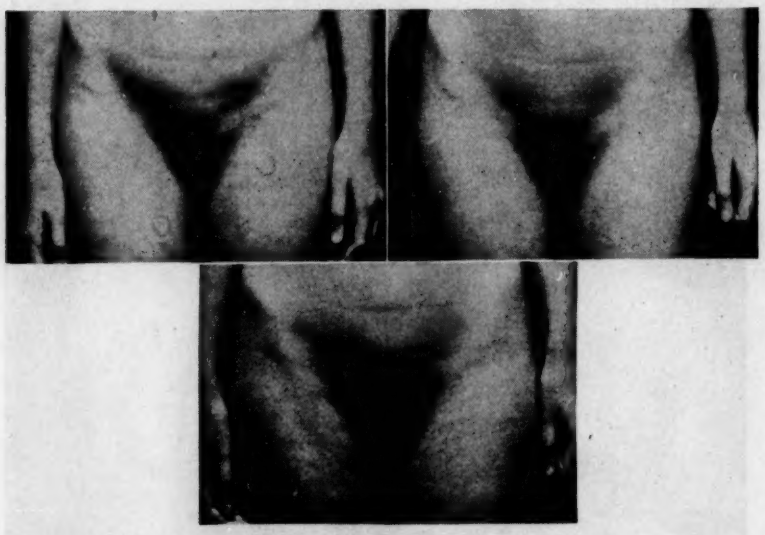

Fig. 4.—Standards for stages in maturation of pubic hair: stages 3, 4, and 5. The infantile stage (1) and the beginning stage (2) are not shown.

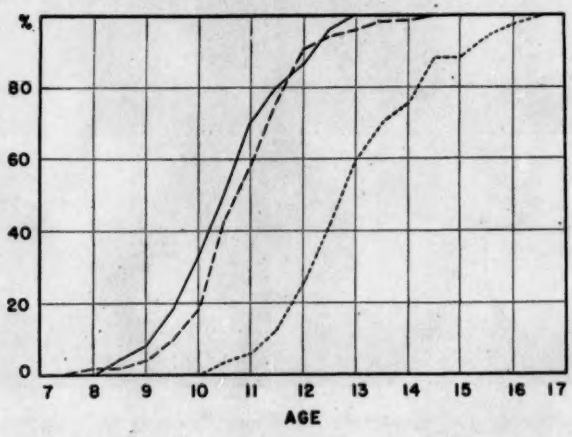

Fig. 5.—Percentage distribution of age at first breast development (indicated by solid line) and age at first appearance of pubic hair (indicated by dashes) in 49 girls and age at menarche (indicated by broken line) in 32 girls.

Actually, then, breast development appears to be more closely related to a maturational event—menarche—appearing on the average over two

years later, than it does to an event—the appearance of pubic hair—appearing on the average only two months later.

It is of some interest to compare beginning maturation—as it is measured by appearance of breasts or of pubic hair, whichever is earlier—with the time elapsing between that event and menarche. Such a comparison is shown in figure 6. Based on the data now available, there appears to be no tendency for early maturing girls to reach menarche in a shorter length of time than late maturing girls. They do, of course, achieve menarche at an earlier age; however, the 5 earliest maturing girls in the series, whose maturation began at the age of 9 or before, took on the average 2.5 years to achieve menarche, while the 5 latest maturing girls, whose maturation began at 12 or after, took on the average 2.3 years to achieve menarche. This problem of duration of maturation will again be discussed in a later section on maturational extremes.

Breast Development: Maturation, Shape, Size and Development of the Areola.—The average ages at the various stages of breast development, as previously defined, were: bud stage, 10.8 years; intermediate stage, 11.4 years; primary mamma stage, 12.2 years; mature stage, 13.7 years. There was, of course, a high association between the stages, the r between any two stages being +0.90 or higher. The distribution of stages, from 8 through 13 years, at which age all girls have passed out of the infantile stage, is as follows:

	Age, Yr.										
Stage	8	8.5	9	9.5	10	10.5	11	11.5	12	12.5	13
1	49	47	45	40	33	25	15	10	7	2	0
2	0	2	2	6	12	14	14	10	5	4	2
3	0	0	2	2	2	6	12	11	8	6	8
4	0	0	0	1	2	4	6	9	12	16	15
5	0	0	0	0	0	0	0	0	0	2	3

Breast size as such was not a factor in the determination of the maturational stage of the breast; that is, at any stage the breast size ranged from small to large. Figure 2 shows girls with small, medium and large breasts at stage 4, the primary mamma stage. The distribution of breast size at this maturational level, using these standards, was: small, 12 girls; medium, 11 girls; large, 9 girls.

Breast shape was also not a factor in the rating of breast development. Figure 3 shows girls, all at the age of menarche, having breast shapes we have called flat, hemispherical and conical.[15] The distribution of breast shape, at menarche, was: flat, 6 girls; hemispherical, 20 girls; conical, 6 girls. The characteristic breast shape attained by an individual girl appears early and maintains itself through the maturational stages, unless broken down by such a factor as early obesity

15. Martin, R.: Lehrbuch der Anthropologie, Jena, Gustav Fischer, 1928.

(fig. 3 *D*). In fact, definitive breast shape can be most easily determined at these early age levels, before the vicissitudes of time and circumstance have broken down the contour, as is particularly true in the case of conical breasts.

The protrusion of the areola as a separate mound above the general level of the breast (primary mamma, stage 4) has been rated in the present series as pronounced, moderate, slight or absent (fig. 7). The areola protrusion for 8 girls was rated as pronounced, for 9 as moderate and for 7 as slight, and 8 did not show this temporary uplift of the areola.

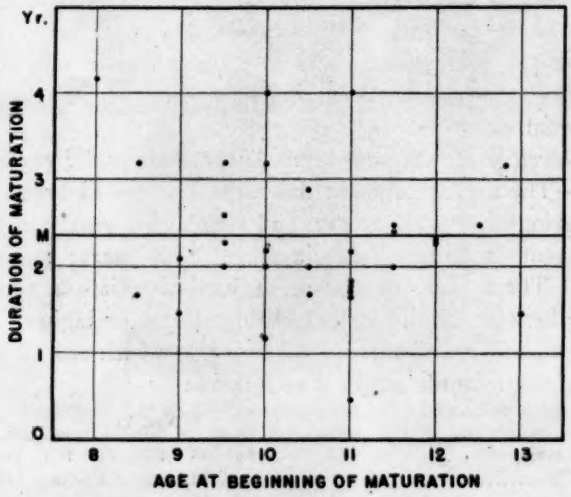

Fig. 6.—Scatter diagram showing age at first appearance of breasts or of pubic hair (whichever is earlier) and time elapsing between this event and menarche; r = —0.11.

The interrelations of breast size, breast shape and presence of the secondary areolar mound at menarche are best seen in tabular form.

		Secondary Areolar Mound				
		Pronounced	Moderate	Slight	None	Total
Small breast (12).....	Flat	0	3	1	1	5
	Hemispherical	2	0	1	3	6
	Conical	1	0	0	0	1
Medium breast (11).....	Flat	0	0	0	0	0
	Hemispherical	2	4	2	1	9
	Conical	1	1	0	0	2
Large breast (9).....	Flat	0	0	0	1	1
	Hemispherical	2	1	2	0	5
	Conical	0	0	1	2	3
Total.....		8	9	7	8	32

The principal associations to be seen may be summarized as follows: Small breasts tend to be flat or hemispherical and, if flat, to lie in the

smaller range of areolar size; medium breasts tend to be hemispherical, with an areola of moderate size; large breasts tend to be hemispherical and to have the areolar mound, or, if conical, not to have the areolar mound.

These associations, based on such a small series, are obviously tentative and must await the collection of a larger quantity of data before definite relations can be established.

Pubic Hair: Maturation; Maturational Asymmetries.—The average ages at the various stages of maturation of the pubic hair, as previously defined, were: stage 2, 11.0 years; stage 3, 11.9 years; stage 4, 12.5 years; stage 5, 13.9 years. There were a moderate association ($r = 0.80$) between stages 2 and 3 and a high association ($r = 0.97$)

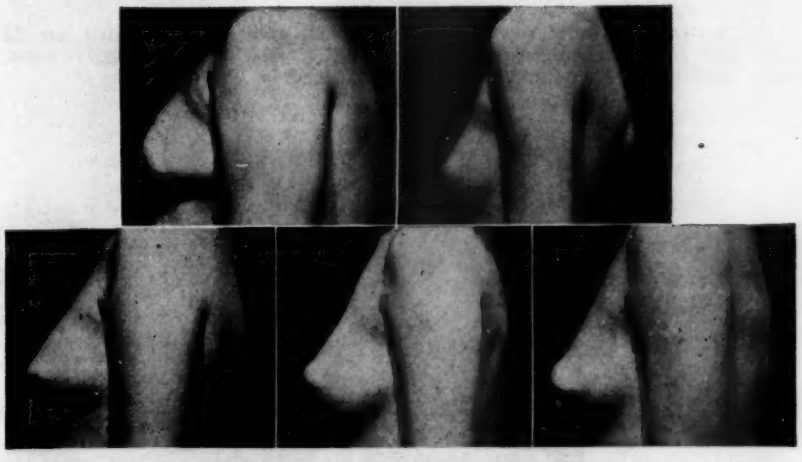

Fig. 7.—Standards for rating degree of secondary areolar protrusion (stage 4 of breast maturation): not rated, due to indented nipple (upper left); none (upper right); and slight, moderate and pronounced (below).

between stages 3 and 4, and 4 and 5. The distribution of stages, from the ages of 8 through 14½ years, at which age all girls had passed through the infantile period, is as follows:

	Age, Yr.													
Stage	8	8.5	9.0	9.5	10	10.5	11	11.5	12	12.5	13	13.5	14	14.5
1.....	48	48	47	44	40	28	21	12	5	3	2	1	1	0
2.....	1	1	2	4	7	16	14	13	12	6	3	3	1	0
3.....	0	0	0	1	1	3	8	11	8	7	3	1	2	2
4.....	0	0	0	0	1	2	5	6	8	14	17	12	7	5
5.....	0	0	0	0	0	0	0	1	0	1	4	6	6	7

Individual differences in maturational patterns have already been mentioned; figure 8 shows 2 girls with asymmetric maturation. Both girls are 12 years of age; in the first girl, breast development is in

stage 4 and pubic hair in stage 3, while in the second girl, breast development is in stage 2 and pubic hair in stage 4.

Menarche: Early and Late Menarche; Individual Differences in Maturational Status at Menarche.—The wide individual differences

Fig. 8.—Individual differences in maturational patterns. Both girls are 12 years old. Left, breast development is in stage 4, pubic hair, in stage 3; right, breast development is in stage 2, pubic hair, in stage 4.

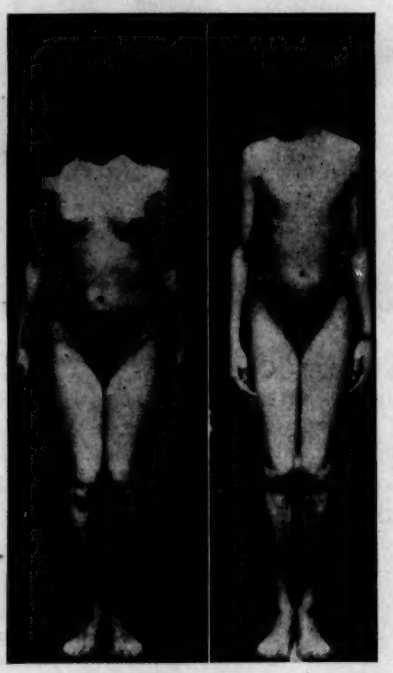

Fig. 9.—Individual differences in sexual maturation as a whole. For the girl at left aged 10.5 years, the breasts and pubic hair are in stage 4; the menarche occurred at 10.5 years. For the girl at right, aged 13.5 years, the breasts and pubic hair are in stage 2; the menarche occurred at 16 years.

which exist in the timing of maturational processes are well shown in figure 9, in which a comparison is made of an early maturing and a

late maturing girl. The early maturing girl had menarche at 10.5 years, at which time both breasts and pubic hair were in the fourth stage of maturation and an adult body configuration was present. The late maturing girl had the menarche at 16 years, and at the age of 13.5 years was in stage 2 for breast development and appearance of pubic hair, with a body configuration still immature.

The majority of the girls in the series were in stage 4 for both breast development and appearance of pubic hair at the time of menarche, regardless of their chronologic age when this event occurred. The distribution of maturational stages at menarche is as follows:

Breast Development, Stage	Appearance of Pubic Hair, Stage	Number of Girls
2	2	0
3	3	1
4	4	18
5	5	1
3	4	1
4	5	2
4	3	4
5	4	1
Other combinations.....		4

Examples of various interrelations of chronologic age, menarche and maturational status are shown in figure 10. The first two illustrations show girls with early (10.3) and late (15.5) menarcheal ages, whose stages of maturation for breast development and appearance of pubic hair (stage 4 in each case) are harmonious for their state of maturity. The third illustration in figure 10 represents the girl most closely approaching the average for our series, with menarche at the age of 12.9 years and with development of both breasts and pubic hair at stage 4. The fourth illustration is that of a girl whose menarche was early (11.5 years) and whose breast development and pubic hair maturation are still immature, although her breast development is just beginning stage 4.

Comparison of Girls Showing Maturational Extremes.—Developmental differences can often be demonstrated by comparing girls taken from opposite ends of a maturational distribution. In this section, the comparisons shown are as follows:

Figure 11: Girls having smallest breast size at menarche (6), compared with girls having largest breast size at menarche (6).

Figure 12: Girls having flat breasts at menarche (6), compared with girls having conical breasts at menarche (6).

Figure 13: Girls having a pronounced secondary areolar mound during maturation (8), compared with girls showing no secondary areolar mound during maturation (8).

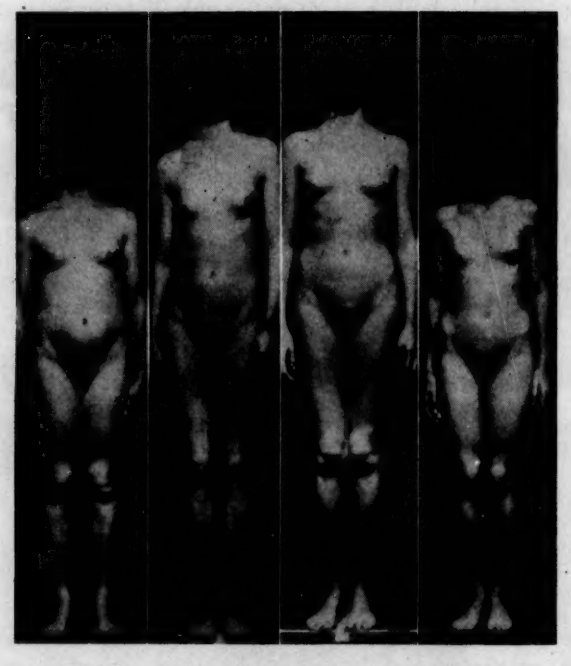

Fig. 10.—Interrelations of chronologic age, menarche and maturational status. All pictures were taken at menarche. First, early menarche (10.3 years), with harmonious (stage 4) development of breasts and pubic hair; second, late menarche (15.5 years) with harmonious (stage 4) development of breasts and pubic hair; third, average menarche (12.9 years), with harmonious (stage 4) development of breasts and pubic hair; fourth, early menarche (11.5 years) with immature (breasts, stage 4 just beginning; pubic hair, stage 3) development of breasts and pubic hair.

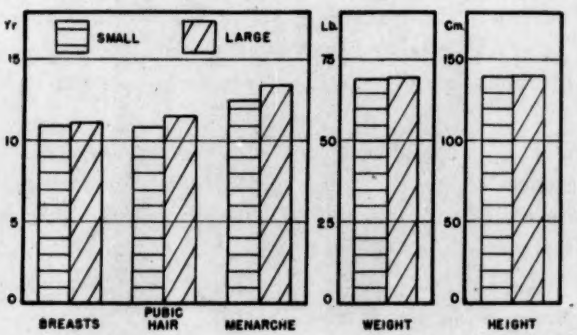

Fig. 11.—Comparison of the 6 girls with smallest breasts and the 6 girls with largest breasts in the series for mean age at first appearance of breasts, mean age at first appearance of pubic hair, mean age at menarche, mean weight at first appearance of breasts and mean height at first appearance of breasts.

Figure 14: Girls whose beginning breast development preceded the first appearance of pubic hair by more than a year (5), compared with girls whose first appearance of pubic hair preceded beginning breast development by more than a year (4).

Figure 15: Girls whose "duration of maturation" (as measured by the time elapsing between age at first appearance of breasts or pubic hair, whichever was earlier, and age at menarche) was long (7), compared with girls for whom this period was short (7).

Each chart shows ages at first appearance of breasts, of pubic hair and of menarche and weight and height at first appearance of breasts. The values charted are the average for each group.

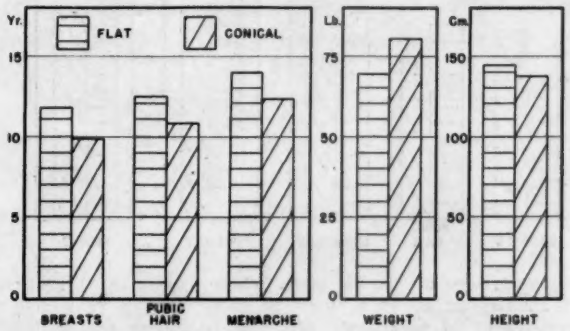

Fig. 12.—Comparison of the 6 girls having breast shape classed as flat and the 6 girls having breast shape classed as conical. See figure 11 for details.

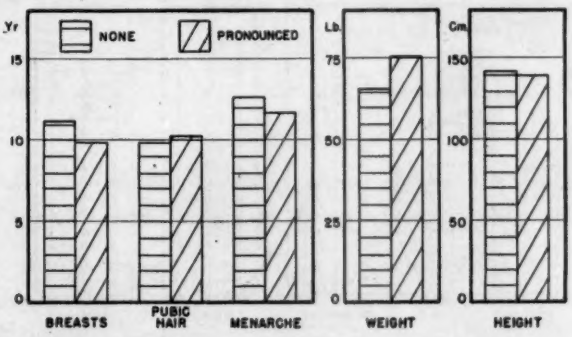

Fig. 13.—Comparison of the 8 girls having a pronounced secondary areolar mound during maturation and the 8 girls having no secondary areolar mound during maturation. See figure 11 for details.

The 6 girls having the smallest breasts at menarche were slightly earlier in age at appearance of breasts (0.2 year), somewhat earlier in age at appearance of pubic hair (0.7 year) and 1.1 year earlier in age at menarche. There was little difference between the groups in weight and height at age of breast development (fig. 11).

Figure 12, comparing flat-breasted and conical-breasted girls, clearly shows the earlier maturation of the latter group. Girls with conical breasts were 2 years earlier in age in breast development, 1.7 years earlier in appearance of pubic hair and 1.7 years earlier in age of menarche. At the age of first appearance of breasts, they were 13 pounds (5.9 Kg.) heavier and slightly shorter than girls whose breast shape was classified as flat.

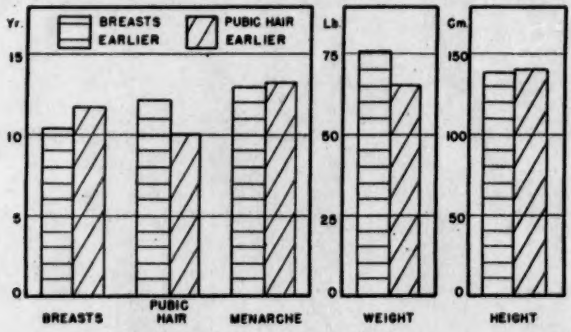

Fig. 14.—Comparison of the 5 girls whose beginning breast development preceded first appearance of pubic hair by more than a year and the 4 girls whose first appearance of pubic hair preceded beginning breast development by more than a year. See figure 11 for details.

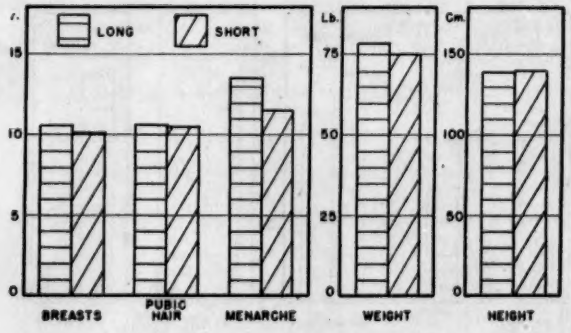

Fig. 15.—Comparison of the 7 girls whose "duration of maturation" was long and the 7 girls for whom this period was short. See figure 11 for details.

Girls showing a pronounced secondary areolar mound during maturation (fig. 13) were earlier in the appearance of breasts (1.3 years) and in age at menarche (1.0 years) but slightly later in appearance of pubic hair (0.4 year). They were 10 pounds (4.5 Kg.) heavier at age of breast development and slightly shorter in height.

Girls whose breast development began more than a year before appearance of pubic hair (fig. 14) showed little difference in age at

menarche from the group in the opposite category, although they were 10 pounds (4.5 Kg.) heavier and slightly shorter.

Girls in whom the "duration of maturation" was long (fig. 15) showed little difference in age at appearance of breasts and age at beginning of development of pubic hair from girls having a short maturational interval. The average duration for the former group was 3.6 years, and that for the latter group, 1.4 years.

Height, Weight and Body Build.—Many studies have been concerned with the relation of sexual maturation to various aspects of height, weight and body build.[11] Sexual maturation has been defined in terms of such criteria as the appearance of certain secondary sexual characteristics, the age at menarche, inflections in the growth cycle,

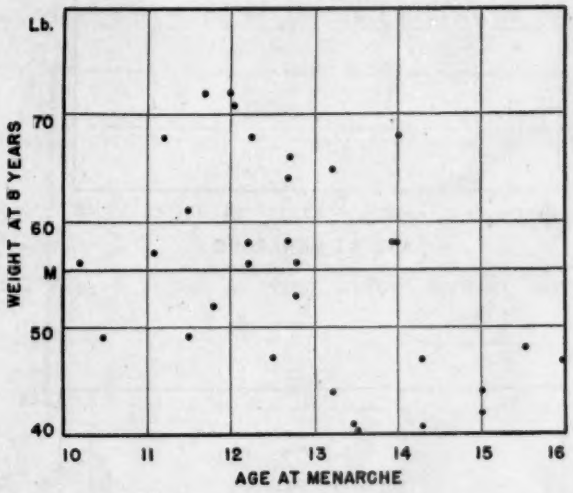

Fig. 16.—Scatter diagram showing weight at age of 8 years and age at menarche.

endocrine status, skeletal development and other indexes of maturation. Body build has been studied in terms both of anthropometric and of descriptive factors.[16] Stuart [9e] recently reviewed a number of important studies in this area.

16. Bayer, L. M.: Build in Relation to Menstrual Disorders and Obesity, Endocrinology **24**:260-268 (Feb.) 1939; Build Variations in Adolescent Girls, J. Pediat. **17**:331-344 (Sept.) 1940; Weight and Menses in Adolescent Girls with Special Reference to Build, ibid. **17**:345-354 (Sept.) 1940. Bullen, A. K., and Hardy, H. L.: Analysis of Body Build Photographs of One Hundred Seventy-Five College Women, Am. J. Phys. Anthropol. **4**:37-68 (March) 1946. Bayley, N., and Bayer, L. M.: The Assessment of Somatic Androgeny, ibid. **4**:433-461 (Dec.) 1946.

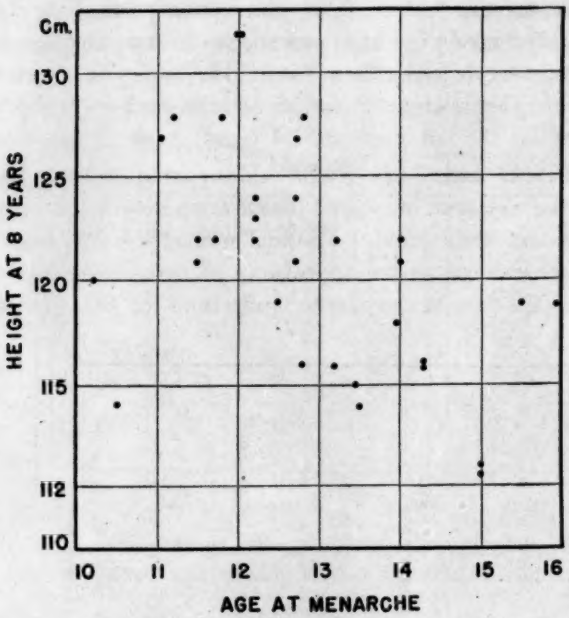

Fig. 17.—Scatter diagram showing height at age of 8 years and age at menarche.

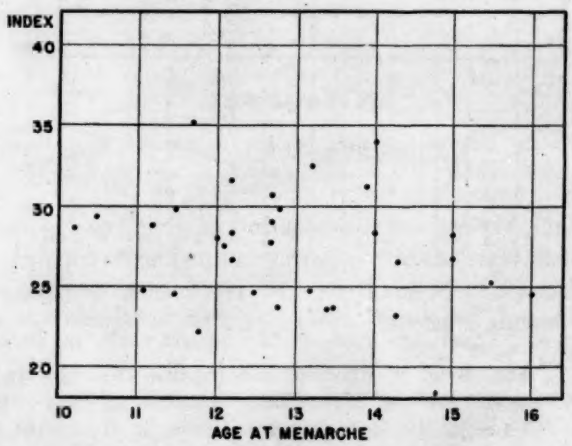

Fig. 18.—Scatter diagram showing weight: height^3 index at age of 8 years and age at menarche.

This section of the present paper will be concerned with only two aspects of a large problem: the relation of weight, height and the weight : height index at 8 years to age at menarche, and the growth progress in weight and height of the earliest maturing and the latest maturing girls in the series.

The relation, in the form of scatter diagrams, is indicated for weight at 8 years and age of menarche (fig. 16), height at 8 years and age at menarche (fig. 17) and weight : height index[3] at 8 years and age at menarche (fig. 18).

From an inspection of these diagrams, certain relations of size and body build at 8 years to time of sexual maturation (as evidenced by menarche) are seen. The tendency for early maturing girls to be larger and stockier at the age of 8 is evident, but it is also interesting to note that girls whose age at menarche was only slightly earlier than the

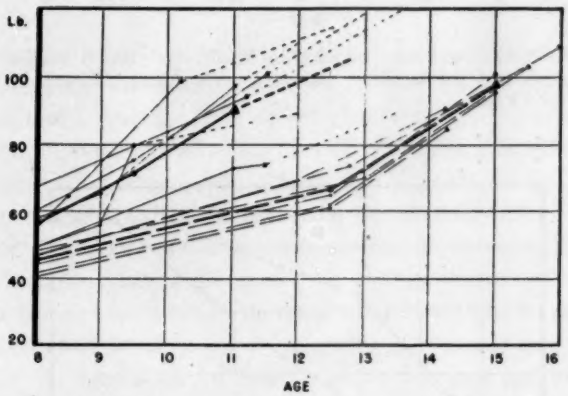

Fig. 19.—Individual growth patterns in weight for the 6 earliest maturing girls (solid lines) and the 6 latest maturing girls (long dashes) in the series. Triangles represent menarche; circles, first breast development; heavy lines, means; short dashes, growth beyond menarche.

average of 12.9 years (those girls between 11.6 and 12.4 years of age) were, in turn, larger and stockier than girls whose age at menarche was early (11.5 years or before). The relations of size and body build at the age of 8 to time of menarche appears, therefore, in the present series to be curvilinear, rather than linear:

	Weight,* Lb.	Height,* Cm.	Index *
Girls having menarche by 11.5 years or earlier (6 girls)....	56.7	122.0	27.3
Girls having menarche between 11.6 and 12.4 years (7 girls)	64.1	126.1	28.6
Girls having menarche at 14.2 years or later (6 girls).....	44.8	115.7	25.7

* Values for girls at 8 years of age.

The average weight for the entire Fels series of 8 year old girls was 55.6 pounds (25.2 Kg.) and the average height, 126.9 cm.

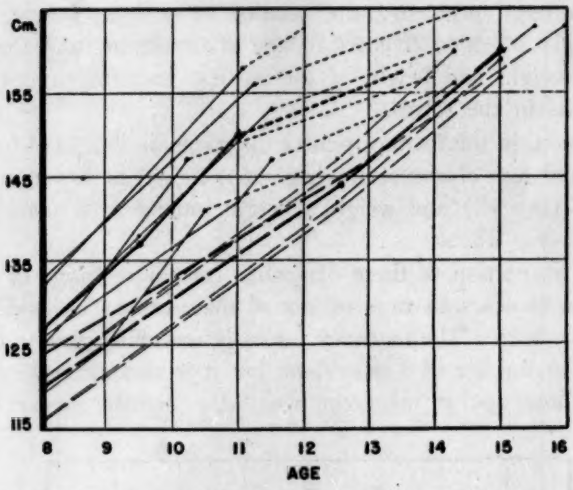

Fig. 20.—Individual growth patterns in height for the 6 earliest maturing girls (solid lines) and the 6 latest maturing girls (long dashes) in the series. See figure 19 for details.

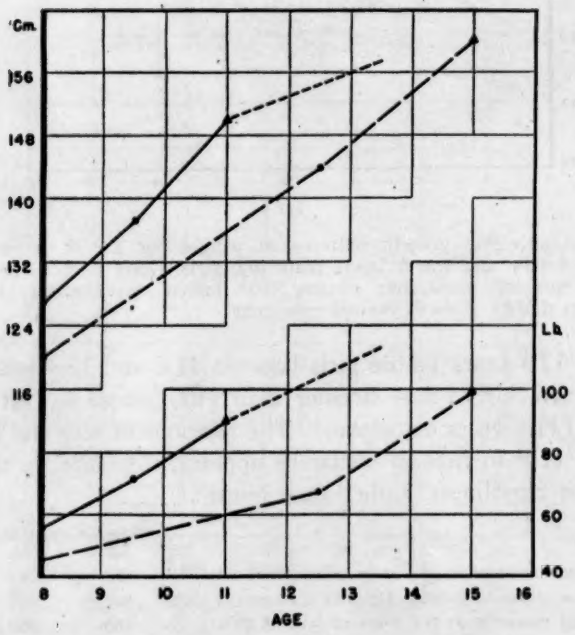

Fig. 21.—Average growth patterns for weight and height, abstracted from figures 19 and 20.

Growth progress, beginning at 8 years, for the 6 earliest maturing girls (average age at menarche, 11 years) and the 6 latest maturing girls (average age at menarche, 15 years) is shown in figure 19 for weight and in figure 20 for height.

Several differences between early and late maturing girls may be seen from an inspection of these graphs: the greater variability in the growth patterns of early maturing girls; the larger size of early maturing girls, when compared according to chronologic age; the smaller size of early maturing girls, when weight and height are compared in terms of menarche; the characteristic differences in growth patterns of early and late maturing girls (fig. 21), resulting in an eventual tendency for convergence of the growth curves. All these phenomena, and others, have been explored in great detail in the studies previously referred to, particularly in the monographs by Shuttleworth.[116-8]

SUMMARY

Various aspects of individual variation in female sexual maturation are described and illustrated, based on an analysis of data obtained from 557 semiannual examinations of 49 girls who are regular participants in the longitudinal growth program of the Fels Research Institute.

Characteristics discussed include the maturation, size, shape and areolar protrusion of the breasts; the development of pubic hair; the advent of menarche, and the interrelations of these maturational features. A comparison is made of girls representing five different types of maturational extremes. The relation of body size to sexual maturation is examined briefly.

Stages of maturation for breasts and pubic hair are illustrated, and the average age at the attainment of the various stages is given, as well as the distribution of the stages at half-yearly age levels. The interrelations of age at first appearance of breasts, age at first appearance of pubic hair and age at menarche are described.

The associations of breast size, breast shape and development of the secondary areolar mound in individual girls are tabulated and discussed.

Individual differences in maturational status at menarche are described; examples of maturational asymmetries are shown, and individual variations in the interrelations of chronologic age, menarche and maturational status are illustrated.

Girls showing maturational extremes in breast size, breast shape, areolar development, maturational sequences and duration of maturation are compared in terms of age at various stages of sexual maturation and in terms of weight and height at age of first breast development.

Two aspects of individual differences in the association of body size with sexual maturation are examined: the relation of weight,

height and weight: height index at 8 years of age to age at menarche and the growth progress of early and late maturing girls.

The observations in the present study are primarily descriptive and classificatory in nature, and the characteristics discussed represent only a portion of the data being collected and analyzed on these same girls. Additional material includes ratings of other secondary sex characters such as axillary hair, the assessment of osseous development and the study of menstrual patterns, differential tissue growth, growth of body segments, physiologic function and endocrine activity during adolescence.

The present study offers, in our opinion, preliminary materials for further research in the variability of human sexual maturation and provides a certain amount of information for the clinician interested in problems of adolescent development.

Antioch College.

SALMONELLA MENINGITIS

Report of Three Cases and Review of One Hundred and Forty-Four Cases From the Literature

LOWELL L. HENDERSON, M.D.
URBANA, ILL.

THE RECENT occurrence in Gorgas Hospital of salmonella meningitis in 2 infants, 1 of whom recovered, prompted the present investigation of this disease. A review of the hospital's clinical and laboratory records back to 1925 revealed a third case, and a review of the literature produced 144 additional cases, which were accepted for the purposes of this paper. Consideration of the characteristics of the disease and of the effects of treatment with sulfonamide compounds should be of interest at present and of use later in evaluating the effectiveness of new preparations, such as streptomycin.

REPORT OF CASES

CASE 1.—R. R., a 3½ month old Negro girl, whose home was in Panamà, Republic of Panama, was brought to the hospital Dec. 8, 1945, because of mucopurulent discharge from the nose and fever of two weeks' duration, and vomiting and listlessness for the past twenty-four hours. The history revealed no previous illness. Birth had been normal and at full term. The diet had consisted of orange juice and a formula of powdered whole milk and "karo" syrup. There had been no diarrhea.

Physical Examination.—The baby weighed 8½ pounds (3,856 Gm.). She appeared acutely ill and dehydrated; the rectal temperature was 103 F. The anterior fontanel was depressed. The pharynx was mildly injected, and there were coarse rales in the lower fields of both lungs, with questionable alteration of the breath sounds in the base of the right lung. The tympanic membranes were normal, and there was no nuchal rigidity. Physical examination otherwise revealed nothing unusual.

Laboratory Data.—The leukocyte count was 5,000 per cubic millimeter, with 28 per cent neutrophils and 72 per cent lymphocytes. The erythrocyte count was 3,400,000. The hemoglobin concentration (Sahli) was 50 per cent. Urinalysis showed nothing remarkable.

Clinical Course.—A tentative diagnosis of pneumonitis and dehydration was made, and treatment was instituted on this basis. Penicillin was given intramuscularly in doses of 10,000 units every three hours. Isotonic solution of sodium chloride, 240 cc., was given by hypodermoclysis on her admission to the hospital, and a like amount was administered the next morning. Twenty-four hours after her admission, the rectal temperature rose to 104 F., the fontanel became tense and the

From the Gorgas Hospital, Ancon, Canal Zone.

neck rigid. A lumbar puncture yielded fluid of a ground-glass appearance, under slightly increased pressure. This fluid was found to contain 1,740 cells per cubic millimeter, of which 94 per cent were neutrophils. Direct smear revealed numerous, plump, gram-negative bacilli. Administration of sodium sulfadiazine, 0.25 Gm. intramuscularly every six hours, was begun. The next day, December 10, the child began passing yellow diarrheal stools, which were submitted for culture. At this time the laboratory reported that the organism cultured from the spinal fluid belonged to the genus Salmonella; shortly thereafter the same organism was isolated from the cultures of the stool. Culture of material obtained from the pharynx did not yield the organism. The use of penicillin was stopped, and the intramuscular administration of sodium sulfadiazine was continued in doses of 0.1 Gm. per pound (450 Gm.) of body weight per day. A transfusion of 80 cc. of fresh whole blood was given on December 13, and nine more transfusions were given by Jan. 22, 1946. These transfusions were well tolerated.

The diarrhea proved of no consequence. Three days after its onset the stools again became normal in appearance and frequency, and after December 15 all cultures were reported negative for organisms of the typhoid-salmonella-dysentery group. During this time the signs of meningeal irritation became more pronounced. Opisthotonos was severe; the deep reflexes were hyperactive, and there were frequent convulsions. This condition gradually improved over a period of ten days, but the opisthotonos persisted to some extent for a month. Culture of spinal fluid obtained on December 26 yielded the same organism as that grown previously. The white cell count at this time was 11,550 per cubic millimeter, with 64 per cent neutrophils and 36 per cent lymphocytes. On December 31 the temperature became normal for the first time. The next day the administration of sulfadiazine was discontinued because the drug was believed at least partially responsible for the infant's poor appetite and frequent vomiting, which had persisted since her admission to the hospital. During the next few days, her appetite improved and the formula was retained well, but the temperature began to rise. Administration of sulfadiazine was reinstituted, and the temperature returned to normal, but the baby began vomiting. This disorder subsided promptly with discontinuance of the sulfadiazine. By January 15 this entire sequence was repeated twice. By that time, the opisthotonos had disappeared, and the baby began to play and to eat normally. The curve for weight, which had shown many reverses, corresponding to the episodes of vomiting, began to rise steadily. The leukocytosis subsided, and the differential count shifted back to a predominance of lymphocytes. The red cell count rose to 3,900,000 per cubic millimeter and the hemoglobin content to 69 per cent (Sahli). On January 25 the cerebrospinal fluid was found to be sterile. It contained 33 cells, mainly lymphocytes, and the glucose and protein values were normal.

On February 5, coincident with an increase in diet, vomiting and fever suddenly recurred. The ears, nose, pharynx and chest all appeared normal on examination. The urine was normal. The white cell count rose to 10,000 per cubic millimeter, with the differential count showing 72 per cent neutrophils. The vomiting and fever subsided after two days, but during the night of February 9 complete paraysis of the left facial nerve appeared. This paralysis was of a peripheral type involving the left side of the face and forehead. Physical and neurologic examinations revealed otherwise a normal condition. Lumbar puncture yielded clear fluid under normal pressure, with normal response to jugular

compression. The cell count showed 7 polymorphonuclear leukocytes per cubic millimeter. Culture of the fluid was sterile. The facial weakness began to improve immediately, and after ten days it was not evident.

The child was observed until March 2, at which time the results of physical examination and laboratory tests were all normal. The weight on her discharge from the hospital was 14 pounds (6,350 Gm.), a gain of 5½ pounds (2,495 Gm.) during the three months in the hospital. The mother was requested to bring the baby to the hospital at monthly intervals for examination. She did so twice, and each time the child appeared healthy and normal in every respect.

Results of Bacteriologic Study.—The Gorgas Hospital Laboratory (Canal Zone Board of Health Laboratory) isolated the organism from the cerebrospinal fluid and specimens of the stools and, as mentioned, identified it as belonging to the genus Salmonella. A culture was then sent to the United States Army Medical School, Washington, D. C., for further study. There the organism was identified as Salmonella newport, with the antigenic structure VI, VIII; e, h; 1, 2, 3.

The patient's blood serum on March 23 did not agglutinate stock cultures of S. newport in any dilution. Furthermore, the organism recovered from the spinal fluid was not agglutinated by the patient's own serum.

CASE 2.—Infant T., a boy, was born in the hospital at full term on May 9, 1946. Delivery was normal, and a mild cyanosis, thought to be due to aspirated mucus, was quickly relieved by the usual methods of resuscitation. The baby weighed 6 pounds 5 ounces (2,863 Gm.) and had a flat nose and prominent inner canthal folds, suggestive of mongolism. Jaundice appeared the next day and gradually deepened. The baby nursed poorly and began to vomit. Feeding by gavage was instituted. Examination of the blood revealed an erythrocyte count of 4,110,000 per cubic millimeter, with a platelet count of 32,880. The hemoglobin content was 80 per cent (Tallqvist). Daily administration of 1 mg. of synthetic vitamin K (menadione U. S. P.) was begun.

On May 14 the baby began passing green diarrheal stools. Respiration became labored, and cyanosis suddenly appeared. The temperature was 100.8 F. A diagnosis of bronchopneumonia was made, which was substantiated by roentgenologic examination. Oxygen therapy was started, and 10,000 units of penicillin was given intramuscularly every three hours. The cyanosis cleared but returned each time an attempt was made to feed the baby by gavage. The next day further laboratory studies revealed an erythrocyte count of 4,250,000 per cubic millimeter and a hemoglobin content of 98 per cent (Sahli). The leukocyte count was 5,000, with 48 per cent neutrophils and 52 per cent lymphocytes. The bleeding time was 2½ minutues and the coagulation time 3½ minutes. One nucleated red blood cell was seen in a stained blood film.

Despite therapy, the attacks of cyanosis became more frequent. These attacks were accompanied with a state of rigidity, and on May 18 the baby exhibited moderate opisthotonos. The temperature began rising steadily, and by the next morning it was 105.6 F. (per rectum), when the child died, at the age of 10 days.

Postmortem Examination.—Pertinent observations included the jaundiced skin and scleras and the mongoloid features, previously mentioned. Cisternal puncture performed aseptically yielded yellow, viscid, turbid cerebrospinal fluid, which was sent to the bacteriologic laboratory for study. Examination of the cranial contents showed a yellow, viscid exudate spread over the base and lateral surfaces and sulci of the brain. There was no gross hemorrhage or degeneration in

the brain; the ventricles were not dilated. The spinal cord appeared normal. The middle ears showed no evidence of suppuration. The interauricular septum of the heart and the membranous portion of the interventricular septum were absent. The lungs appeared normal. No lesions were observed in the bowel.

Microscopic examination of the brain showed that the pia was lifted from the cortex by a thick layer of neutrophilic and mononuclear leukocytes. The meningeal and cortical vessels were extremely congested. The brain appeared normal. Sections of the spinal cord showed a thin layer of exudate, similar to that over the brain. There was no evidence of pneumonia in the lungs.

Anatomic Diagnoses.—The following diagnoses were made: mongolism, acute suppurative meningitis, congenital heart disease, cor triloculare biventriculare, defect of the interventricular septum, generalized icterus and congestion of the liver and spleen.

Results of Bacteriologic Study.—Culture of the cerebrospinal fluid yielded an organism of the genus Salmonella which was identified by the United States Army Medical School as Salmonella typhimurium.

CASE 3.—M. H., a Negro girl 13 months of age, was admitted to Gorgas Hospital on July 18, 1935, because of fever and lethargy of three days' duration. Inquiry revealed that she had had a persistent cough for several days and no bowel movement for two days. The past history was not significant.

Physical Examination.—The child appeared poorly nourished, acutely ill and dehydrated. The rectal temperature was 104.8 F. Breath sounds throughout both pulmonary fields were rough, and coarse rales were audible in the bases of both lungs. Physical examination otherwise showed nothing abnormal.

Laboratory Data.—The erythrocyte count was 2,600,000 per cubic millimeter, and the hemoglobin content was 40 per cent (Sahli). The leukocyte count was 16,800, with 71 per cent neutrophils and 29 per cent lymphocytes. Smears of the blood revealed no malarial parasites. Urinalysis and examinations of the stool showed nothing abnormal.

Clinical Course.—The patient received symptomatic and supportive treatment, and at first she seemed to improve; the appetite was better, and she appeared less fretful. The leukocyte count dropped to a normal level on July 23. The temperature, however, remained elevated, and on July 25 signs of meningeal irritation appeared. Lumbar puncture was performed, which yielded clear fluid under normal pressure. The cell count was 930 per cubic millimeter, of which 93 per cent were lymphocytes. No organisms were found on smear, and the culture was reported to be sterile. The reaction for globulin was positive, and there was 26 mg. of glucose per hundred cubic centimeters. A second specimen of spinal fluid obtained two days later was cloudy; it contained 1,200 cells per cubic millimeter and showed a predominance of neutrophils. Examination of the blood at this time showed leukocytosis, with a count of 11,300 cells and 76 per cent neutrophils.

The child continued to cough, eat poorly, vomit frequently and lose weight. The signs of meningeal irritation became more pronounced, and death occurred on Aug. 12, 1935.

Postmortem Examination.—The middle ears were filled with mucoid, yellowish pus. The cerebrospinal fluid was increased in amount and was cloudy. Thick, yellow pus occupied the subdural space, covering the brain and filling the sulci. The convolutions of the brain were flattened, and the frontal areas were soft and injected. There was thick, yellow pus in both lateral ventricles around the

choroid plexuses. Specimens of spinal fluid and of pus from the middle ears and the meninges were saved for bacteriologic study. The lungs showed scattered areas of bronchopneumonia. No other pertinent observation was made.

Microscopic examination of the dura showed the stromas to be edematous, and on the inner surface there was a thick layer of exudate, containing predominantly polymorphonuclear leukocytes. A section of cortex showed edema and cellular exudation in the leptomeninges, with engorgement of the vessels. The surface of the brain was edematous, and there was some perivascular infiltration of polymorphonuclear leukocytes. Sections from other parts of the brain showed the same type of perivascular infiltration. The leptomeninges of the cord also showed edema and cellular exudate. The gross diagnosis of bronchopneumonia was confirmed on microscopic examination of sections of the lungs.

Anatomic Diagnoses.—The following diagnoses were made: acute suppurative meningitis, acute suppurative encephalitis, secondary to the meningitis; acute bilateral mucopurulent otitis media and bilateral bronchopneumonia.

Results of Bacteriologic Study.—Smears of the material taken from each middle ear showed Staphylococcus aureus, Neisseria catarrhalis and gram-negative bacilli. Smears of spinal fluid contained a great number of pus cells and many gram-negative bacilli, some of which were intracellular. Culture of the spinal fluid resulted in the identification of the organism as a member of the genus Salmonella. Because of the lack of facilities for proper identification of the type, the culture tube was sealed and filed. Eleven years later, when a number of old cultures were submitted to the Army Medical School for further identification, the organism from this case was found to be Salmonella panama, with the antigenic structure I, IX, XII; 1, v; 1, 5.

REVIEW OF THE LITERATURE

An attempt was made to collect all the reported cases of salmonella meningitis for which enough data are available to warrant further study. To facilitate classification, the organism involved in each case is referred to by the name now in common usage. If this term differs significantly from that used in the original article, the original term follows in parentheses.

The first report of meningitis due to an organism of the genus Salmonella was made by Ghon[1] in 1907 at the Kongress für Hygiene. He stated that he had seen 2 cases of "metastatic meningitis" in young children with enteritis, caused by bacilli of the paratyphoid group. One of the bacilli was identified as Salmonella paratyphi B. The other was characterized by its ability to form indole, which makes questionable its identity as a member of the salmonella group, although not definitely precluding its membership.[2]

From 1907 to 1925 sporadic reports appeared which will be mentioned later in this paper. In 1925, Brahdy[3] reported a case of his own

1. Ghon: Die Bazillen der Typhusgruppe, in XIV Internationalen Kongress für Hygiene und Dermographie (1907), 1908, vol. 4.

2. Bornstein, S.: The State of the Salmonella Problem, J. Immunol. **46**:439-496 (June) 1943.

3. Brahdy, M. B.: A Case of Meningitis Caused by the Bacillus Paratyphosus B, Arch. Pediat. **42**:550-553 (Aug.) 1925.

and reviewed 9 cases mentioned in seven preceding reports. In 1930, Lynch and Shelburne [4] collected 15 cases in the literature, to which they added their own, making a total of 16.

The first comprehensive review, by Bahrenburg and Ecker,[5] appeared in 1937. In presenting a case that they had observed, these authors commented on the reports of 34 cases of salmonella meningitis which they found in the literature. They pointed out that for accurate classification of the salmonella organisms certain serologic procedures are necessary. Fifteen of the reports did not include enough material to satisfy their criteria. The following paragraph is a résumé of the cases which they accepted, with references to the other sources, occasionally the original article, from which additional information was obtained.

Symmers and Wilson,[6] 1909, a child aged 4 months, Salmonella enteritidis, no enteritis, fatal outcome; Hundeshagen,[7] 1918, a child aged 3 months, S. paratyphi B, fatal outcome; Lesné,[8] 1920, a soldier aged 25, S. paratyphi B, with enteric fever, recovery; Smith and Aberd,[9] 1921, boy aged 5 weeks, S. enteritidis, fatal outcome; Cooke and Bell,[10] 1922, boy aged 10 weeks, type of Salmonella undetermined, fatal outcome; Brahdy,[3] 1925, girl aged 13 months, S. paratyphi B, diarrhea and bronchopneumonia, fatal outcome; Stuart and Krikorian,[11] 1926, boy aged 11 years, S. enteritidis, fatal outcome; Pesch,[12] 1926, child a few weeks old, S. enteritidis, fatal outcome; Pansini,[8] 1927, girl aged 9 years, Salmonella paratyphi A, fatal outcome; Claudius, 1928, boy aged 4 months, S. enteritidis, fatal outcome; Lynch and Shelburne,[4] 1930, girl aged 1 year, S. enteritidis, fatal outcome; Rojas, 1931, S. paratyphi A, fatal outcome; Malossi and Ara,[13] 1931, child aged 6

4. Lynch, B., Jr., and Shelburne, S. A.: Paratyphoid-Enteritidis Meningitis: Report of Additional Case Due to Bacillus Enteritidis, Am. J. M. Sc. **179**:411-418 (March) 1930.

5. Bahrenburg, J. H., and Ecker, E. E.: Meningitis Due to Organisms Belonging to Salmonella Group, J. Infect. Dis. **60**:81-87 (Jan.-Feb.) 1937.

6. Symmers, W. S. C., and Wilson, W. J.: On Three Cases of Cerebrospinal Meningitis, Associated Respectively with Bacillus Anthracis, Bacillus Typhosus and Bacillus Enteritidis (Gaertner), J. Path. & Bact. **13**:251-255, 1909.

7. Cited by Brahdy [3] and by Lynch and Shelburne.[4]

8. Cited by Lynch and Shelburne.[4]

9. Smith and Aberd, cited by Lynch and Shelburne [4] and by Rieper.[27]

10. Cooke, J. V., and Bell, H. H.: The Incidence of Meningitis in Early Infancy, with a Description of Two Cases Due to Unusual Organisms, Am. J. Dis. Child. **24**:387-396 (Nov.) 1922.

11. Stuart, G., and Krikorian, K. S.: Meningitis Due to B. Enteritidis Gaertner, J. Hyg. **25**:160-164 (July) 1926.

12. Pesch, cited by Rieper.[27]

13. Malossi and Ara, cited by Cid and Gonzalez.[19d]

months, S. enteritidis, fatal outcome; Márquez and Curbelo,[14] 1931, child aged 13 years, S. enteritidis, fatal outcome; Jundell,[15] 1933, boy aged 2 months, S. paratyphi B, diarrhea, fatal outcome; Stevenson and Wills,[16] 1933, girl aged 9 weeks, S. enteritidis, diarrhea, fatal outcome; Schmitt,[17] 1934, boy aged 3 months, S. enteritidis, fatal outcome; Vaughn,[18] 1934, girl aged 15 months, S. enteritidis, fatal outcome; Rupert, 1934, S. enteritidis, fatal outcome, and Bahrenburg and Ecker,[5] 1937, boy aged 7 weeks, S. paratyphi B, fatal outcome.

The following reports are the fifteen which Bahrenburg and Ecker mentioned but did not include:

Artz and Boese, 1908, 2 cases, 1 in a child aged 5 months, the other in a child aged 7 weeks. There is disagreement as to the identity of the organisms, the one in the first case having been referred to as S. paratyphi B[19] or S. enteritidis,[20] and the organism in the second case as S. paratyphi B,[21] S. enteritidis[20a] or an undetermined type.[22] Both children died, and intestinal lesions were observed post mortem. Eckert,[7] 1910, infant aged 8 months, S. paratyphi A, fatal outcome, enteric lesions observed at autopsy; Tolmer and Weissenbach,[8] 1915, adult aged 25 years, S. paratyphi A with enteritis, fatal outcome; Walterhöfer,[7] 1917, soldier aged 20 years, S. paratyphi B with enteritis, recovery; Opitz,[23] 1919, child aged 15 months, meningococcic meningitis, followed by meningitis due to S. enteritidis, fatal outcome; Blechmann,[24] 1922, 2 cases in infants, S. paratyphi B with enteritis, recovery; Caronia and Auricchio,[8] 1922, 2 cases, 1 in a child 9 years old (S. paratyphi A),

14. Márquez, R., and Curbelo, A.: Primer caso, en Cuba, de meninigitis purulenta a bacilo enteritidis de Gaertner, Rev. méd. cubana **42**:1129-1135 (Oct.) 1931.

15. Jundell, cited by Mulhern, M. E., and Seelye, W. B.: A Case of Meningitis in a Newborn Infant Due to a Slow Lactose Fermenting Organism Belonging to the Colon Bacillus Group, J. Lab. & Clin. Med. **21**:793-797 (May) 1936.

16. Stevenson, F. H., and Wills, L. K.: Primary Meningitis Due to the Gärtner Bacillus, Lancet **2**:1084-1086 (Nov. 11) 1933.

17. Schmitt, P.: Ueber einen Fall von Gehirnhautentzündung durch Bacterium enteritidis Gärtner, Monatschr. f. Kinderh. **59**:269-271, 1934.

18. Vaughn, J. O.: Bacillus Enteritidis Meningitis in an Infant of Fifteen Months, J. Pediat. **4**:631-635 (May) 1934.

19. (*a*) Schmidt, B.: Paratyphus-B-Meningitis bei einem Säugling, Klin. Wchnschr. **17**:303-304 (Feb. 26) 1938. (*b*) Brahdy.[3] (*c*) Lynch and Shelburne.[4] (*d*) Cid, R. L., and Gonzalez, R. M.: Meningitis a Salmonellas paratíficas, Rev. chilena de pediat. **15**:660-674 (Aug.) 1944.

20. (*a*) Crozier, T. H.: Meningitis Due to Bact. Enteritidis (Gaertner), Ulster M. J. **7**:261-262 (Oct.) 1938. (*b*) Lynch and Shelburne.[4]

21. Cid and Gonzalez.[19d] Schmidt.[19a]

22. Brahdy.[3] Lynch and Shelburne.[4]

23. Opitz, cited by Stevenson and Wills.[16]

24. Blechmann, cited by Brahdy.[3]

and the other in a child 6 years old (S. paratyphi B) both with enteric fever and both recovering; Voigt,[7] 1922, infant aged 9 days, S. paratyphi B, fatal outcome; Artom, 1923, S. paratyphi B, meningoencephalitis, fatal outcome; Appelbaum,[25] 1925, boy aged 7 months, meningococcic meningitis, followed by meningitis due to S. paratyphi B, fatal outcome; Linden, 1930, boy aged 4 months, S. enteritidis, fatal outcome; Anderson,[26] 1932, boy aged 5 weeks, S. paratyphi B with enteritis, fatal outcome; Rieper,[27] 1933, boy aged 3½ months, S. enteritidis, fatal outcome, and Schulz-Schmidtborn,[28] 1934, infant aged 9 months, S. enteritidis, fatal outcome.

The following reports of other cases prior to 1937 were not mentioned previously:

Teveli,[29] 1930, infant aged 6 weeks, S. typhimurium (Bacterium enteritidis breslau), meningitis and furunculosis, fatal outcome; Souper, Smith and Stephen,[30] 1930, girl aged 3½ months, S. enteritidis var. dublin, fatal outcome (this case was included in a review of salmonella infections by Smith[31] in 1933); Kuttner and Zepp,[32] 1932, man, Salmonella choleraesuis (monophasic Salmonella suipestifer), fatal outcome; Hayasaka,[33] 1933, S. enteritidis in 2 men aged 36 and 44, respectively, who were receiving malaria therapy for syphilis of the central nervous system, fatal outcome in both cases; Smith,[34] 1934, boy

25. Appelbaum, E.: A Case of Meningitis Caused by the Meningococcus and the Paratyphoid B Bacillus, Arch. Pediat. **42**:607-609 (Sept.) 1925.

26. Anderson, T.: Case of Meningitis Caused by Bacillus Paratyphosus B, Lancet **1**:183 (Jan. 23) 1932.

27. Rieper, P.: Eitrige Meningitis durch Bacillus Enteritidis Gärtner, Virchows Arch. f. path. Anat. **289**:301-311, 1933.

28. Schulz-Schmidtborn: Meningitis durch Bacterium enteritidis Gärtner, München. med. Wchnschr. **81**:1976-1977 (Dec. 20) 1934.

29. Teveli, Z.: Der Bacillus Breslaviensis als Erreger der Furunkulose und der eitrigen Hirnhautentzündung im Säuglingsalter, Jahrb. f. Kinderh. **126**:197-203 (Jan.) 1930.

30. Souper, H. R.; Smith, J., and Stephen, J. A.: Three Sporadic Cases of Infection Due to Salmonella Type Dublin, Arch. Dis. Childhood **5**:271-274 (Aug.) 1930.

31. Smith, J.: Sporadic Infections in Aberdeen Due to Food Poisoning Organisms of the Salmonella Group, J. Hyg. **33**:224-232 (April) 1933.

32. Kuttner, A. G., and Zepp, H. D.: Paratyphoid-Like Fever in Children Due to Salmonella Suipestifer Group, Bull. Johns Hopkins Hosp. **51**:373-387 (Dec.) 1932.

33. Hayasaka, C.: Im Verlauf einer Malariakur durch Bacillus enteritidis Gärtner entstandene Meningitis und Sepsis, Tohoku J. Exper. Med. **21**:466-504 (Sept. 22) 1933.

34. Smith, J.: Sporadic Salmonella Infections: A New Salmonella Type, J. Hyg. **34**:351-360 (Oct.) 1934.

aged 7 months, S. enteritidis var. dublin, fatal outcome; Habs,[35] 1934, girl aged 1½ years, S. enteritidis, fatal outcome; Chiari,[36] 1934, 2 infants with S. enteritidis, a girl aged 16 months, with diarrhea, pneumonia and left hemiparesis, fatal outcome, and a girl aged 4 months, with enteritis and bilateral otitis media, fatal outcome; Craig,[37] 1936, infant aged 20 days, type of Salmonella undetermined, fatal outcome; Boycott and McNee,[38] 1936, woman aged 35, S. choleraesuis (S. suipestifer) fatal outcome, and Wildführ,[39] 1936, girl aged 8 weeks, S. enteritidis, fatal outcome. The case of Fothergill and Sweet,[40] 1933, which was mentioned by several authors, probably was due to an organism of the colon group, as they suggested, rather than to one of the salmonellas.

From the available information in the cases mentioned in the preceding paragraphs, little was learned concerning the therapeutic measures employed. Supportive and symptomatic treatment was given, and occasional mention was made of administration of antimeningococcus serum U.S.P. Although blood transfusions may have been given, no reference to such procedure was discovered. The reports from 1937 to the present furnished more information and merit more consideration.

In 1937, Ravitch and Washington [41] described the case of a 4 year old girl whose spinal fluid on the first examination contained meningococci, but which twenty-four hours later, on the third culture, yielded S. choleraesuis. During the following sixteen days, cultures of both the blood and the spinal fluid yielded that organism. Diarrhea was present part of the time, but cultures of the feces and the urine were negative for the organisms. Treatment consisting in blood transfusions,

35. Habs, H.: Zur Typendifferenzierung in der Salmonellagruppe, Ztschr. f. Hyg. u. Infektionskr. **116**:537-549, 1934.

36. Chiari, H.: Ueber die "invasiven Fähigkeiten" des Bakterium enteritidis Gärtner, insbesondere seine Rolle als Erreger eitriger Entzündungen, Wien. klin. Wchnschr. **47**:1511-1513 (Dec. 14) 1934.

37. Craig, W. S.: Meningitis in the Newborn, Arch. Dis. Childhood **11**:171-186 (Aug.) 1936.

38. Boycott, J., and McNee, J. W.: Human Infection with American Hog-Cholera Bacillus: A Third Example in England, Lancet **2**:741-742 (Sept. 26) 1936.

39. Wildführ, G.: Bacterium enteritidis Gärtner als Erreger einer Gehirnhautentzündung, Deutsche med. Wchnschr. **62**:344 (Feb. 28) 1936.

40. Fothergill, L. D., and Sweet, L. K.: Meningitis in Infants and Children, with Special Reference to Age-Incidence and Bacteriologic Diagnosis, J. Pediat. **2**:696-710 (June) 1933.

41. Ravitch, M. M., and Washington, J. A.: Suipestifer Septicemia and Meningitis Complicating Meningococcic Septicemia and Meningococcic Meningitis, J. A. M. A. **109**:1122-1123 (Oct. 2) 1937.

repeated spinal punctures and forced drainage resulted in a cure after forty-eight days. The authors, in a review of S. choleraesuis meningitis, mentioned a case reported by Materna and Januschke in the German literature in 1925. This report was on a man whose death was due to purulent meningitis. At postmortem examination, cultures of the blood and of the material from the spleen, gallbladder and meninges yielded S. choleraesuis.

Cure was effected in the case reported by Storey [42] in 1938. The patient, a man, aged 23, was hospitalized because of a fever which continued for several weeks. There were no signs referable to the abdomen or the bowel, but culture of the stool on the fiftieth day yielded S. paratyphi B and continued to yield the organism for twenty-seven days. Signs of meningitis appeared on the sixty-sixth day, and culture of the spinal fluid yielded S. paratyphi B. Treatment was symptomatic. By the seventy-sixth day the meningitis had subsided, and the patient was discharged from the hospital shortly afterward. Schmidt,[19a] in the same year, described a case of S. paratyphi B meningitis with a fatal outcome in a 6 week old baby. Death took place after an illness of six days. Another case of meningitis due to the same organism in an infant was described by Gordon and Kennedy [43] in 1938. The baby, 21 days of age, died after an illness of eleven days. No diarrhea had been noted. Postmortem examination revealed purulent meningitis and encephalitis. Crozier,[20a] in 1938, described the clinical course of an illness in a boy 2½ months of age in whom fever and vomiting had been prominent symptoms since his vaccination against smallpox fifteen days before. On his admission to the hospital, signs of meningeal irritation were noted, and the spinal fluid contained 350 cells per cubic millimeter, mainly neutrophils. Culture of the fluid yielded S. enteritidis. The infant died in a convulsion three days later. S. enteritidis var. jena was demonstrated in a case reported by Röhn [44] in the same year. The child, who was 6 months of age, died in six days. An example of mixed infection was reported by Welcker and Vogl [45] in 1938. Their patient, a 5½ month old girl, was found on her admission to the hospital to have meningococci in

42. Storey, W. E.: Purulent Meningitis Complicating Paratyphoid Fever: Report of a Case with Recovery, J. M. A. Georgia **27**:472-474 (Dec.) 1938.

43. Gordon, H., and Kennedy, J. A.: Bacterium Paratyphosum B Meningitis, Am. J. Clin. Path. **8**:170-178 (March) 1938.

44. Röhn, C.: Seltene Enteritis-Gärtner-Erkrankungen beim Säugling und Kleinkind (D8), Arch. f. Kinderh. **115**:137-145, 1938.

45. Welcker, A., and Vogl, H.: Meningitis bei einem Säugling, verursacht durch Meningokokken und Bac. enteritidis Breslau, zugleich ein Beitrag zur Frage der pathogenen Eigenschaften der Breslau-Bacillen, Klin. Wchnschr. **17**: 852-854 (June 11) 1938.

the spinal fluid. Antimeningococcus serum U.S.P. was given. Two weeks after admission S. typhimurium (Bacterium enteritidis breslau) was cultured from the spinal fluid. Five days later the child died after a convulsion. Observations at autopsy confirmed the diagnosis. One other report in 1938 bears mention. Clifton and Werner [46] described a case of subdural abscess due to S. choleraesuis in a 10 month old girl, who recovered after surgical drainage of the abscess. Although the lumbar spinal fluid contained 20 cells per cubic millimeter and culture yielded the organism, the condition was not primarily meningitis and is not included in the present tabulation.

Guthrie and Montgomery [47] in 1939 reported an epidemic of meningitis due to S. enteritidis in newborn babies.

> The most constant initial symptom was inability to suck, and this was quickly followed by vomiting (sometimes projectile), diarrhea, convulsions, coma and death, the total duration of symptoms varying from one to five days.

In all cases the outcome was fatal. Postmortem examination showed purulent meningitis with greenish yellow pus in 10 cases and congestion and edema of the meninges in 3 more, cultures of which yielded the organism. In all cases there was a catarrhal enteritis, always limited to the small intestine. In addition, in a number of the cases evidence of cholecystitis was exhibited, the contents of the gallbladder in 4 of the infants being frankly purulent. The authors mentioned 2 more cases of meningitis with a fatal outcome, 1 in a 5 month old baby, due to S. typhimurium, and the other in a 9 month old boy, due to S. enteritidis var. dublin. Both infants had diarrhea and signs of meningeal irritation. The authors stated that in all their cases there was clinical evidence of hematogenous spread. In 1939, Abramson, Frant and Oldenbusch [48] also reported 2 cases of meningitis, due to S. panama. One was in a girl 9 days of age and the other in a boy 2 weeks old. Both infants died. Study of the organism by Schiff, of New York, and Kauffman, of Copenhagen, Denmark, resulted in its proper identification.

In 1940, Ramón Guerra, Peluffo and Aleppo,[49] in a comprehensive review of salmonella meningitis, collected 59 cases, each of which has

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46. Clifton, W. M., and Werner, M.: Infections with Salmonella Suipestifer (Hog Cholera Bacillus) in Childhood, with Report of a Case of Bilateral Subdural Abscess Ending in Recovery, Am. J. Dis. Child. **55**:553-558 (March) 1938.

47. Guthrie, K. J., and Montgomery, G. L.: Infections with Bacterium Enteritidis in Infancy, with Triad of Enteritis, Cholecystitis and Meningitis, J. Path. & Bact. **49**:393-409 (Sept.) 1939.

48. Abramson, H.; Frant, S., and Oldenbusch, C.: Salmonella Infection of the Newborn: Its Differentiation from Epidemic Diarrhea and Other Primary Enteric Disorders of the Newborn, M. Clin. North America **23**:591-606 (May) 1939.

49. Ramón Guerra, A.; Peluffo, E., and Aleppo, P. L., in Bonaba, J., and others: Estudios sobre la etiología infecciosa de las diarreas infantiles, Montevideo, Garcia Morales, 1940, pp. 91-130.

already been mentioned except for the 2 of their own. In both these cases with fatal outcomes, the organism was S. typhimurium; 1 case was that of an 8 month old infant and the other that of a 6 month old boy. In the latter case, described in detail in another report,[50] tuberculous mesenteric adenitis was observed at autopsy. The authors later included these 2 cases in a review of salmonella infections in children.[51]

Wengeler [52] in 1940 reported 3 cases of meningitis due to S. enteritidis var. jena in infants, aged 3, 5 and 8 weeks, respectively. All the cases were fatal, and no mention was made of chemotherapy. In a brief review of the subject, the author included 2 cases of salmonella meningitis reported by Hertel in 1939, 1 in an adult, aged 24, due to S. choleraesuis, and the other in a 5 year old girl, due to S. typhimurium (Bacterium enteritidis breslau). Presumably, both cases had a fatal outcome. He also referred to a case reported by Ackermann and Froboese and to 1 reported by Wameling. However, the former case [53] was 1 of sepsis; at autopsy S. enteritidis was cultured from material from the brain, lungs, spleen, liver and kidney. The clinical picture was not that of meningitis. The other case [54] was included in a bacteriologic study from the Koch Institute in 1937, and no information was given except that culture of the spinal fluid of a sick infant yielded S. enteritidis var. kiel. It was probably a case already reported from the clinical aspect. In 1940, Katsampes and Bradford [55] reported the first recovery from meningitis due to S. panama. Their patient was a girl 1 month of age, who was treated with blood transfusions and sulfapyridine. After apparent recovery, there was a relapse, from which she recovered completely. In 1940 also, Meyer-Rohn [56] described a case of meningitis in a 1 year old child which was fatal in five days, despite treatment with a sulfonamide preparation. The organism was identified as S. enteritidis var. kiel.

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50. Peluffo, E.; Ramón Guerra, A., and Aleppo, P. L.: Meningitis supurada en un lactante, con cultivo de salmonela "typhi murium" en el líquido Céfalo-raquídeo, Arch. de pediat. d. Uruguay **11**:48-52 (Jan.) 1940.

51. Hormaeche, E.; Peluffo, C. A., and Aleppo, P. L.: Las salmonelas en patología infantil, Pediat. Américas **3**:90-101 (Feb. 15) 1945.

52. Wengeler, F.: Drei Meningitisfälle bei Säuglingen durch Bakterium enteritidis Gaertner Typ Jena, Med. Klin. **36**:1217-1218 (Nov. 1) 1940.

53. Ackermann, G., and Froboese, C.: Sepsis durch Bacillus paratyphosus enteritidis Breslau und Gärtner, Klin. Wchnschr. **18**:1311-1315 (Oct. 7) 1939.

54. Wameling, J.: Zur Frage der kulturellen Typendiagnose der enteritidis Gärtner-Bazillen, Zentralbl. f. Bakt. (Abt. 1) **139**:297-301 (July 12) 1937.

55. Katsampes, C. P., and Bradford, W. L.: Recovery from Salmonella (Panama) Meningitis in Infant Treated with Sulfapyridine, J. Pediat. **16**:79-85 (Jan.) 1940.

56. Meyer-Rohn, J.: Meningitis durch Bacterium enteritidis Gärtner, Deutsche med. Wchnschr. **66**:1193-1194 (Oct. 25) 1940.

In 1941, Curbelo and Martínez Cruz [57] reviewed the work resulting from an epidemic of meningitis in newborn infants in Cuba in late 1936 and early 1937, during which 21 infants died. Aballí and his associates [58] in 1937 had reviewed 12 of these cases, presenting the clinical and pathologic observations, and Sánchez Santiago [59] reported on 3 more in 1938. In a typical case the infant showed bulging of the fontanel, hyperactive reflexes, convulsions, fever and diarrhea with slimy, fetid stools, with death in one to three days and discovery of thick, purulent basilar exudate at autopsy. The same organism, which was thought at first to be S. typhimurium (Salmonella aertrycke), was cultured from the spinal fluid of each infant, and from the blood and stools of a few. Curbelo and Martínez Cruz [57] stated that further study of the organism by the New York Salmonella Center disclosed that it was not S. aertrycke, but a previously undescribed type, to which the same S. havana was given. Details of the bacteriologic study were reported by Schiff and Saphra.[60] Lyon and Folsom [61] in 1941 reported a case of meningitis in a 2½ year old boy, due to an organism which they identified as S. choleraesuis (S. suipestifer). Recovery followed intensive therapy, with administration of sulfanilamide both orally and intrathecally. The authors stated that organisms from subcultures sent to the Harriet Lane Home did not show the motility of the original organisms, and that, therefore, they were called Hemophilus influenzae. They did not, however, feel that the clinical course was that of an influenzal meningitis. Furthermore, Bornstein [2] observed that salmonella organisms in subculture show numerous variations, including loss of motility. It is unfortunate that the studies were not in agreement, but it is felt that the case should be included in the present tabulation.

In 1941, Guthrie and Anderson [62] described a double infection in a girl 14 months of age. At first, pure cultures of meningococci were obtained from the spinal fluid. With sulfathiazole therapy, the signs of meningitis disappeared, and the cultures became sterile for organisms.

57. Curbelo, A., and Martínez Cruz, J. A.: Historia de la Salmonella havana, Arch. de med. inf. **10**:170-179 (July-Sept.) 1941.

58. Aballí, A. A.; Falcón, S.; Sala Panisello, F.; Curbelo, A., and Martínez, Cruz, J. A.: Salmonelosis del recién nacido, Bol. Soc. cubana de pediat. **9**:123-160 (April) 1937.

59. Sánchez Santiago, B.: Meningitis a Salmonela, Arch. de med. inf. **7**: 188-191 (Jan.-March) 1938.

60. Schiff, F., and Saphra, I.: A New Salmonella Type: Salmonella Havana, J. Infect. Dis. **68**:125-127 (March-April) 1941.

61. Lyon, G. M., and Folsom, T. G.: Meningitis Due to Salmonella Suipestifer (Case Report), West Virginia M. J. **37**:249-255 (June) 1941.

62. Guthrie, K. J., and Anderson, T.: Double Infection of the Meninges with Meningococcus and Gaertner's Bacillus, Brit. M. J. **1**:193-194 (Feb. 8) 1941.

Two weeks later the meningitis reappeared, and S. enteritidis was recovered from the spinal fluid. A week later the child died. Apparently, no sulfonamide preparation was given after discovery of the salmonella organism. Wilsdon and Gibson [63] in 1941 reported 1 of the few cases of salmonella meningitis in adults. Their patient was a man, aged 61, who lived sixteen days. S. london was isolated from the spinal fluid on three different occasions.

Patterson [64] in 1942 reported on 2 patients with S. paratyphi B meningitis, both of whom recovered. One patient was a boy 8 years of age and the other a girl, aged 5 months. Both children received sulfapyridine and sulfathiazole. In 1942, Valledor, García Pérez and Pedrera [65] reported the recovery of a 3 month old baby from meningitis due to Salmonella eastbourne. The child was treated with sulfadiazine. After one relapse the disease did not recur, but residual mental changes were noted. In that year also, Bray and Meredith [66] reported a case of subdural abscess in a boy 4½ months of age. The organism isolated was Salmonella san diego. The infant died, despite treatment with sulfathiazole, sulfapyridine and blood transfusions. This case, like that of Clifton and Werner,[46] does not belong in the group discussed in the present paper.

In 1944, Cid and Gonzalez [19d] reported from Chile 4 cases of salmonella meningitis, 2 caused by S. paratyphi A and 2 by S. paratyphi B. Of the cases due to the former organism, 1 was that of a boy 9 months of age who received sulfadiazine and blood transfusions and recovered. The other case was also one of a boy aged 9 months; he received sulfathiazole and blood transfusions but died. Of the cases of meningitis due to S. paratyphi B, 1 was that of a girl 3 months of age who received sulfadiazine and blood transfusions and recovered. The other case was that of a girl 4 months of age who received only blood transfusions at first; then, after a prolonged illness, she received sulfathiazole but died. In a review of the subject, the authors referred to another case of the disease, due to S. enteritidis, which occurred in Chile and which was evidently reported locally in 1942 by Costa and Gaete. Since no further information was given and no original reference could be found, there is no reason to credit it in this review.

63. Wilsdon, K. F., and Gibson, A.: Meningitis Due to Salmonella London, Lancet **1**:665-666 (May 24) 1941.

64. Patterson, W. H.: Paratyphoid B Meningitis: Two Cases Which Recovered, Lancet **1**:678-679 (June 6) 1942.

65. Valledor, T.; García Pérez, E., and Pedrera, J.: Meningitis purulenta a Salmonela Eastbourne en un lactante de tres meses, tratado con sulfadiazina: Evolución curativa después de una recaída, Bol. Soc. cubana de pediat. **14**:413-429 (Aug.) 1942.

66. Bray, W. E., and Meredith, J. M.: Fatal Salmonella Intracranial Infection in an Infant: Report of a Case, J. Lab. & Clin. Med. **28**:152-156 (Nov.) 1942.

Tomic-Karovic and Kovacevic [67] in 1944 reported a fatal case of meningitis due to S. enteritidis in a child a few weeks of age. Diarrhea was present, but no record of examination of the stool was included. Hollis and Barron [68] in 1944 reported a case of meningitis due to Salmonella oranienburg in a 5 week old boy. There was no evidence of enteritis. Despite treatment with blood transfusions and sulfathiazole, the infant died on the fifty-fourth day. Neter [69] in 1944 presented an extensive review of salmonella meningitis and added a case of his own, that of a 3 year old girl who died of S. choleraesuis meningitis, although treated with sulfadiazine. Included in his review was a case reported by Caselli and Teobaldo, of Argentina, in 1939. Their patient was an infant with S. paratyphi B meningitis, which proved fatal.

Wood, Mayfield and Frisch [70] in 1945 reported on 2 infants with S. panama meningitis who were treated with sulfadiazine. One of these children, a 23 day old boy, recovered, but the other, a girl 21 days of age, died.

High and Spalding [71] in 1946 reported on another patient who recovered from meningitis due to S. panama. The patient was a 2½ month old boy who was treated with sulfadiazine. Blindness, deafness and weakness of an extremity were residual. The authors mentioned an unpublished report by Leeder on 10 cases of fatal meningitis, also due to S. panama; all the patients were infants whose exact ages were not known. Barnes [72] reported a case of meningitis due to S. choleraesuis in a 2 week old girl. Diarrhea had been present before her admission to the hospital. The baby was treated, first, with sulfamerazine, penicillin and blood transfusions and, later, with a limited amount of streptomycin, but death occurred fifty-four days after admission. Gradual enlargement of the head and the results of a ventricular puncture shortly before death led to the conclusion that an internal hydrocephalus had developed. Rodaniche [73] recently reported a fatal case of S. newport meningitis in a 39 year old man. Treatment consisted in administration of penicillin and sulfadiazine.

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67. Tomic-Karovic, K., and Kovacevic, N.: Bakterium enteritidis Gärtner als Ursache einer Meningitis, Wien. klin. Wchnschr. **56**:716 (Dec. 17) 1943; abstracted, Bull. Hyg. **19**:648 (Aug.) 1944.

68. Hollis, C. H., and Barron, E. W.: Meningitis Due to Salmonella Oranienburg: Report of Case, J. Pediat. **24**:568-573 (May) 1944.

69. Neter, E. R.: Salmonella Cholerae Suis Meningitis: Report of Case and Review of Literature on Salmonella Meningitis, Arch. Int. Med. **73**:425-429 (May) 1944.

70. Wood, W. H., Jr.; Mayfield, F. H., and Frisch, A. W.: Meningitis Due to Salmonella Panama, J. A. M. A. **128**:868-870 (July 21) 1945.

71. High, R. H., and Spalding, E. H.: Human Infection with Salmonella Panama, Am. J. Dis. Child. **72**:181-188 (Aug.) 1946.

72. Barnes, M.: Salmonella Meningitis: Report of a Case Treated with Streptomycin, Bull. Charlotte Mem. Hosp. **2**:44-47 (Sept.) 1946.

73. Rodaniche, A.: Arch. d. Hosp. Santo Tomas, to be published.

Reports from salmonella centers have included several cases of salmonella meningitis. Seligmann, Saphra and Wassermann,[74] of the New York Salmonella Center, stated in 1943 that they had typed salmonellas from 15 specimens of spinal fluid which they had received. These types included: S. typhimurium, 3 specimens; S. choleraesuis, 3; S. eastbourne, 2; S. panama, 2, and Salmonella derby, S. oranienburg, S. enteritidis, Salmonella anatum and S. havana, each from 1 specimen. In a recent report[75] these authors mentioned an additional case of S. choleraesuis meningitis and 1 of S. paratyphi B meningitis. Edwards and Bruner,[76] of the Kentucky Salmonella Center, in 1943 listed 3 cases of salmonella meningitis, and Edwards[77] in 1944 reported another case. Recently, Edwards stated[78] that at the Kentucky Center a total of 9 cultures of salmonella have been typed from cases of meningitis; S. oranienburg from 2 cultures; S. panama from 3, and Salmonella bareilly, Salmonella loma-linda, S. anatum and Salmonella new brunswick, each from 1 culture. Much of this material represents cases which have been reported separately and which are mentioned previously. Of the other cases, so little is known as to make their inclusion of slight interest, except for notation of the additional types of organisms involved: S. anatum, S. bareilly, S. derby, S. loma-linda and S. new brunswick. Seligmann[74] also mentioned an epidemic of S. typhimurium meningitis in newborn infants, with 6 fatalities, from which he received material. Since he pointed out[79] that these cases will not be reported elsewhere, they are included in the present review.

The recent report of the National Research Council on streptomycin[80] included 2 cases of salmonella meningitis of an unnamed type. One of the patients recovered. The other patient, who died, may be 1 in the report by Barnes which has already been mentioned.

Table 1 presents in chronologic order all the cases of salmonella meningitis which were accepted for the purposes of this paper.

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74. Seligmann, E.; Saphra, I., and Wassermann, M.: Salmonella Infections in Man: Analysis of One Thousand Cases Bacteriologically Identified in New York Salmonella Center, Am. J. Hyg. **38**:226-249 (Nov.) 1943.

75. Seligmann, E.; Saphra, I., and Wassermann, M.: Salmonella Infections in the U. S. A.; A Second Series of Two Thousand Human Infections Recorded by the N. Y. Salmonella Center, J. Immunol. **54**:69-87 (Sept.) 1946.

76. Edwards, P. R., and Bruner, D. W.: Occurrence and Distribution of Salmonella Types in United States, J. Infect. Dis. **72**:58-67 (Jan.-Feb.) 1943.

77. Edwards, P. R.: Salmonella Loma-Linda: A New Type Isolated from Meningitis, Proc. Soc. Exper. Biol. & Med. **57**:104-106 (Oct.) 1944.

78. Edwards, P. R.: Personal communication to the author.

79. Seligmann, E.: Personal communication to the author.

80. Streptomycin in the Treatment of Infections: A Report of One Thousand Cases, Committee on Chemotherapeutics and Other Agents, National Research Council, J. A. M. A. **132**:4-11 (Sept. 7) 1946.

TABLE 1.—*Chronologic Listing of 147 Cases of Salmonella Meningitis, with Type of Organism, Age and Sex of Patient and Outcome of the Disease*

Author	Year	Organism	Sex of Patient	Age of Patient	Outcome
Ghon [1]	1907	S. paratyphi B	?	Infant	Fatal
Arzt and Boese, cited by Bahrenburg and Ecker [5]	1908	Undetermined	?	5 mo.	Fatal
		Undetermined	?	7 wk.	Fatal
Symmers and Wilson [6]	1909	S. enteritidis	?	4 mo.	Fatal
Eckert [7]	1910	S. paratyphi A	?	8 mo.	Fatal
Tolmer and Weissenbach [8]	1915	S. paratyphi A	?	25 yr.	Fatal
Walterhöfer [7]	1917	S. paratyphi B	M	20 yr.	Recovery
Hundeshagen [7]	1918	S. paratyphi B	?	3 mo.	Fatal
Opitz [23]	1919	Meningococcus	?	15 mo.	Fatal
		S. enteritidis			
Lesné [8]	1920	S. paratyphi B	M	25 yr.	Recovery
Smith and Aberd [9]	1921	S. enteritidis	M	5 wk.	Fatal
Cooke and Bell [10]	1922	Undetermined	M	10 wk.	Fatal
Blechmann [24]	1922	S. paratyphi B	?	Infant	Recovery
		(2 cases)	?	Infant	Recovery
Caronia and Auricchio [8]	1922	S. paratyphi A	?	9 yr.	Recovery
		S. paratyphi B	?	6 yr.	Recovery
Voigt [7]	1922	S. paratyphi B	?	9 days	Fatal
Artom, cited by Bahrenburg and Ecker [5]	1923	S. paratyphi B	?	?	Fatal
Appelbaum [25]	1925	Meningococcus	M	7 mo.	Fatal
		S. paratyphi B			
Brahdy [3]	1925	S. paratyphi B	F	13 mo.	Fatal
Materna and Januschke, cited by Ravitch and Washington [41]	1925	S. choleraesius	M	Adult	Fatal
Stuart and Krikorian [11]	1926	S. enteritidis	M	11 yr.	Fatal
Pesch [12]	1926	S enteritidis	?	Few weeks	Fatal
Pansini [3]	1927	S. paratyphi A	F	9 yr.	Fatal
Claudius, cited by Bahrenburg and Ecker [5]	1928	S. enteritidis	M	4 mo.	Fatal
Teveli [29]	1930	S. typhimurium	?	6 wk.	Fatal
Souper, Smith and Stephen [30]	1930	S. enteritidis var. dublin	F	3½ mo.	Fatal
Lynch and Shelburne [4]	1930	S. enteritidis	F	1 yr.	Fatal
Linden, cited by Bahrenburg and Ecker [5]	1930	S. enteritidis	M	4 mo.	Fatal
Rojas, cited by Bahrenburg and Ecker [5]	1931	S. paratyphi A	?	?	Fatal
Malossi and Ara [13]	1931	S. enteritidis	?	6 mo.	Fatal
Márquez and Curbelo [14]	1931	S. enteritidis	?	13 yr.	Fatal
Kuttner and Zepp [32]	1932	S. cholerasuis	M	Adult	Fatal
Anderson [26]	1932	S. paratyphi B	M	5 wk.	Fatal
Hayasaka [33]	1933	S. enteritidis	M	36 yr.	Fatal
		(2 cases)	M	44 yr.	Fatal
Rieper [27]	1933	S. enteritidis	M	3½ mo.	Fatal
Jundell [15]	1933	S. paratyphi B	M	2 mo.	Fatal
Stevenson and Wills [16]	1933	S. enteritidis	F	9 wk.	Fatal
Schmitt [17]	1934	S. enteritidis	M	3 mo.	Fatal
Vaughn [18]	1934	S. enteritidis	F	15 mo.	Fatal
Rupert, cited by Bahrenburg and Ecker [5]	1934	S. enteritidis	?	?	Fatal
Schulz-Schmidtborn [28]	1934	S. enteritidis	?	9 mo.	Fatal
Smith [34]	1934	S. enteritidis var. dublin	M	7 mo.	Fatal
Habs [35]	1934	S. enteritidis	F	1½ yr.	Fatal
Chiari [36]	1934	S. enteritidis	F	16 mo.	Fatal
		(2 cases)	F	4 mo.	Fatal
Craig [37]	1936	Undetermined	?	20 days	Fatal
Boycott and McNee [38]	1936	S. choleraesuis	F	35 yr.	Fatal

TABLE 1.—*Chronologic Listing of 147 Cases of Salmonella Meningitis with Type of Organism, Age and Sex of Patient and Outcome of the Disease—Continued*

Author	Year	Organism	Sex of Patient	Age of Patient	Outcome
Wildführ [39]	1936	S. enteritidis	F	8 wk.	Fatal
Bahrenburg and Ecker [5]	1937	S. paratyphi B	M	7 wk.	Fatal
Ravitch and Washington [41]	1937	Meningococcus S. choleraesuis	F	4 yr.	Recovery
Storey [42]	1938	S. Paratyphi B	M	23 yr.	Recovery
Schmidt [10a]	1938	S. paratyphi B	?	6 wk.	Fatal
Gordon and Kennedy [43]	1938	S. paratyphi B	?	21 days	Fatal
Crozier [20a]	1938	S. enteritidis	M	2½ mo.	Fatal
Röhn [44]	1938	S. enteritidis var. jena	?	6 mo.	Fatal
Welcker and Vogl [45]	1938	Meningococcus S. typhimurium	F	5½ mo.	Fatal
Caselli and Teobaldo, cited by Neter [69]	1939	S. paratyphi B	?	Infant	Fatal
Hertel, cited by Wengeler [53]	1939	S. choleraesuis	?	24 yr.	Fatal
		S. typhimurium	F	5 yr.	Fatal
Guthrie and Montgomery [47]	1939	S. enteritidis (12 cases)	?	Newborn	Fatal
		S. typhimurium	?	5 mo.	Fatal
		S. enteritidis var. dublin	M	9 mo.	Fatal
Abramson, Frant and Oldenbusch [48]	1939	S. panama	F	9 days	Fatal
		(2 cases)	M	2 wk.	Fatal
Ramón Guerra, Peluffo and Aleppo [49]	1940	S. typhimurium	?	8 mo.	Fatal
		(2 cases)	M	6 mo.	Fatal
Wengeler [53]	1940	S. enteritidis	?	3 wk.	Fatal
		var. jena	?	5 wk.	Fatal
		(3 cases)	?	8 wk.	Fatal
Katsampes and Bradford [55]	1940	S. panama	F	1 mo.	Recovery
Meyer-Rohn [56]	1940	S. enteritidis var. kiel	?	1 yr.	Fatal
Curbelo and Martinez Cruz [57]	1941	S. havana (21 cases)	?	Newborn	Fatal
Lyon and Folsom [61]	1941	S. choleraesuis	M	2½ yr.	Recovery
Guthrie and Anderson [62]	1941	Meningococcus S. enteritidis	F	14 mo.	Fatal
Wilsdon and Gibson [63]	1941	S. london	M	61 yr.	Fatal
Patterson [64]	1942	S. paratyphi B	M	8 yr.	Recovery
		(2 cases)	F	5 mo.	Recovery
Valledor, García Pérez and Pedrera [65]	1942	S. eastbourne	?	3 mo.	Recovery
Cid and Gonzalez [10d]	1944	S. paratyphi A	M	9 mo.	Recovery
		(2 cases)	M	9 mo.	Fatal
		S. paratyphi B	F	3 mo.	Recovery
		(2 cases)	F	4 mo.	Fatal
Tomic-Karovic and Kovacevic [67]	1944	S. enteritidis	?	Few weeks	Fatal
Hollis and Barron [68]	1944	S. oranienburg	M	5 wk.	Fatal
Neter [69]	1944	S. choleraesuis	F	3 yr.	Fatal
Wood, Mayfield and Frisch [70]	1946	S. panama	M	23 days	Recovery
		(2 cases)	F	21 days	Fatal
High and Spalding [72]	1946	S. panama	M	2½ mo.	Recovery
Leeder, cited by High and Spalding [71]	1946	S. panama (10 cases)	?	Infants	Fatal
Barnes [73]	1946	S. choleraesuis	F	2 wk.	Fatal
Rodaniche [73]	1946	S. newport	M	30 yr.	Fatal
Henderson, present report	1946	S. newport	F	3½ mo.	Recovery
		S. typhimurium	M	Newborn	Fatal
		S. panama	F	13 mo.	Fatal
Seligmann, Saphra and Wassermann [75]	1948	S. typhimurium (6 cases)	?	Newborn	Fatal
		S. anatum	?	?	Fatal
		S. derby	?	?	Fatal
Edwards and Bruner [76]	1948	S. bareilly	?	?	Unknown
		S. loma-linda	?	?	Unknown
		S. new brunswick	?	?	Unknown

COMMENT

The salmonella problem has in the past been attended with considerable misunderstanding and lack of clarity. According to the concepts of the Kiel doctrine,[2] there were two groups of salmonella organisms, those of animal origin, capable of causing no more than a mild gastroenteritis in man and those pathologic for man, causing a typhoid-like fever. Comparatively few types were identified with the latter group. This small number of pathologic types is reflected by the data in table 1, which shows that four types of organisms accounted for all the cases of salmonella meningitis until 1935.

During the past decade much progress has been made. The establishment of salmonella centers has made possible the collection of enough material for a systematic study. Intensive investigation has resulted in improved methods of type identification and, consequently, in more accurate classification. New types of both human and animal origin are constantly being identified. More and more of the salmonella organisms of animal origin have been discovered pathologic for man. Hormaeche, Peluffo and Aleppo,[81] who noted this in their study of diarrheas of infants, stated that the Kiel doctrine was not applicable to that age group. Their concept has become known as the "doctrine of Montevideo." [81] Bornstein,[2] in his excellent review of the salmonella problem, concluded that it would be "fair to assume that all types of salmonellas are potentially pathologic for man." He urged abandonment of the old idea that a particular type of infection was caused by a certain type of salmonella organism, and he suggested the division of salmonella infections into three groups on a clinical basis, regardless of the type of organism: (1) gastroenteritis, manifested by vomiting, diarrhea and mild fever for a few days; (2) salmonella fever, milder than typhoid, but with positive blood cultures and fever for one to three weeks, and (3) septicemia, characterized by high remittent fever, positive blood cultures and localization in any part of the body. Either of the first two types may occasionally give rise to a septicemia. Meningitis is the result of a particular localization of the septic process.

On the basis of Bornstein's classification, any organism of the genus Salmonella might be expected to cause meningitis, but those with the greatest tendency to produce septicemia should predominate. Such an apparent predilection for the meninges was noted in two earlier reports. Smith [84] in 1934 mentioned S. enteritidis var. dublin and S. choleraesuis, and Guthrie and Anderson [62] in 1941 named S. enteritidis and S. enteritidis var. dublin as common offenders. Table 2 shows

81. Ramón Guerra, A.; Peluffo, E.; LaGuarda, M., and Aleppo, P. L.: Septicemias y bacteriemias por salmonelas en el lactante, Arch. de pediat. d. Uruguay **10**:669-682 (Nov.) 1939.

TABLE 2.—*Cases of Salmonella Meningitis Classified by Type of Organism and Age of Patient* *

Type of Organism	Age			
	Under 1 Month	1 Month or Over	Unknown	Total
S. paratyphi A	..	6	1	7
	—	—	—	—
	..	2	0	2
S. paratyphi B	2	19	1	22
	—	—	—	—
	0	9	0	9
S. typhimurium	7	6	..	13
	—	—	—	—
	0	0	..	0
S. derby	..	..	1	1
	—	—	—	—
	..	..	0	0
S. choleraesuis	1	7	..	8
	—	—	—	—
	0	2	..	2
S. oranienburg	..	1	..	1
	—	—	—	—
	..	0	..	0
S. bareilly	..	..	1	1
	—	—	—	—
	..	..	0	0
S. newport	..	2	..	2
	—	—	—	—
	..	1	..	1
S. enteritidis	12	24	1	37
	—	—	—	—
	0	0	0	0
S. enteritidis var. jena, dublin, etc	1	7	..	8
	—	—	—	—
	0	0	..	0
S. eastborne	..	1	..	1
	—	—	—	—
	..	1	..	1
S. panama	4	3	10	17
	—	—	—	—
	1	2	0	3
S. loma-linda	..	..	1	1
	—	—	—	—
	..	..	0	0
S. london	..	1	..	1
	—	—	—	—
	..	0	..	0
S. anatum	..	..	1	1
	—	—	—	—
	..	..	0	0
S. new brunswick	..	..	1	1
	—	—	—	—
	..	..	0	0
S. havana	21	..	..	21
	—	—	—	—
	0	..	..	0
Types undetermined	1	3	..	4
	—	—	—	—
	0	0	..	0
Total	49	80	18	147
	—	—	—	—
	1	17	0	18

* The numerator shows the number of cases in each category, and the denominator, the number of recoveries.

the incidence of each type of salmonella in the group of cases collected in the present report. S. enteritidis and its varieties accounted for 45 cases; S. paratyphi B, for 22; S. havana, for 21; S. panama, for 17; S. typhimurium, for 13; S. choleraesuis, for 8, and each of the other organisms, for 7 or less. A total of sixteen types and numerous type variations are represented, but, although it is possible that eventually all types of salmonella may actually be found capable of causing meningitis, it is likely that the trend will continue in the present direction, with a few types responsible for the majority of the cases.

In accounting for the occurrence of salmonella meningitis, a second factor of importance is the decrease in tissue resistance. Bornstein [2] stated that in septicemia the predilection for locus minoris resistentiae was evident. Neter [69] emphasized that diminished resistance was an important factor in the pathogenesis of salmonella meningitis. This observation is well demonstrated in the many cases in which the meningitis was superimposed on other conditions that had already weakened the meninges. Meningococcic meningitis preceded the salmonella infection in 5 cases. Two more cases occurred during treatment of syphilitic infection of the central nervous system. The most striking example, however, is seen in newborn infants who have been subjected to the trauma of birth and who possess, as Cooke and Bell [10] pointed out, a high permeability of the intestinal mucosa and a low resistance to bacterial infection. The peculiar susceptibility of the newborn can well explain the epidemic spread of the disease through the nurseries of maternity centers, which has occurred on at least three occasions, accounting for more than one fourth of the 147 cases collected.

Ramón Guerra and his associates,[49] in a review of 59 cases of salmonella meningitis, called attention to the uniform picture presented by that disease in the newborn. They pointed out that in their series it was characterized by a tendency to occur in epidemic form, running a rapidly fatal course, with diarrhea a prominent symptom. At autopsy lesions of the bowel and extraintestinal localizations were observed, as well as involvement of the meninges. In contrast to the uniform picture in this age group, they noted that the disease in older infants and in children occurred only sporadically, diarrhea might not be present, lesions of the bowel were infrequent, the course was less acute and there were seldom foci other than in the meninges. The observations in the present review have been consistent with their conclusions. To complete the description of the disease, it should be mentioned that other symptoms common to both age groups included fever, leukocytosis, variable agglutination reactions, pleocytosis, with predominance of neutrophils, and a tendency to a basilar distribution of the purulent exudate, as observed at autopsy. The signs of meningeal irritation were usually prominent in children of the older age group but were less pronounced

in the newborn. Craig,[37] in a study of meningitis in newborn infants, observed the difficulty of diagnosis. He emphasizeed that after the first week of life any intracranial disturbance, such as ocular incoordination, nystagmus or restless movements of the head should always suggest meningitis.

The prognosis of the disease is considerably influenced by the age of the patient, as both Ramón Guerra and his associates [40] and Craig [37] suggested. No instance of recovery has been observed in the newborn, and of the 49 patients under 1 month of age recovery occurred only

TABLE 3.—*Cases of Salmonella Meningitis in Which a Sulfonamide Preparation was Administered*

Author	Year	Type of Organism	Age	Treatment	Outcome
Katsampes and Bradford [55]	1940	S. panama	1 mo.	Sulfapyridine, blood transfusion	Recovery
Meyer-Rohn [56]	1940	S. enteritidis var. kiel	1 yr.	Sulfonamide, vitamin K [53]	Fatal
Lyon and Folsom [61].....	1941	S. choleraesuis	2½ yr.	Sulfanilamide	Recovery
Guthrie and Anderson [62]..	1941	Meningococci	14 mo.	Sulfathiazole	Fatal
Patterson [64]	1942	S. enteritidis			
		S. paratyphi B	8 yr.	Sulfathiazole	Recovery
		(2 cases)	5 mo.	Sulfapyridine	Recovery
Valledor, García Pérez and Pedrera [65]	1942	S. eastborne	3 mo.	Sulfadiazine	Recovery
Cid and Gonzalez [194].....	1944	S. paratyphi A	9 mo.	Sulfadiazine, blood transfusion	Recovery
		(2 cases)	9 mo.	Sulfathiazole, blood transfusion	Fatal
		S. paratyphi B	3 mo.	Sulfadiazine, blood transfusion	Recovery
		(2 cases)	4 mo.	Sulfathiazine, blood transfusion	Fatal
Hollis and Barron [68].....	1944	S. oranienburg	5 wk.	Sulfathiazole, blood transfusion	Fatal
Neter [69]	1944	S. choleraesuis	3 yr.	Sulfadiazine	Fatal
Wood, Mayfield and Frisch [70]	1945	S. panama	23 days	Sulfadiazine	Recovery
		(2 cases)	21 days	Sulfadiazine	Fatal
High and Spalding [71]....	1946	S. panama	2½ mo.	Sulfadiazine	Recovery
Barnes [72]	1946	S. choleraesuis	2 wk.	Sulfamerazine, penicillin, blood transfusion, streptomycin,	Fatal
Rodaniche [73]	1946	S. newport	39 yr.	Sulfadiazine, penicillin	
Henderson, present report	1946	S. newport	3 mo.	Sulfadiazine, blood transfusion	Recovery

in the 23 day old infant reported on by Wood, Mayfield and Frisch [70] (table 3). On the other hand, of 80 infants 1 month of age, or older, 17 recovered. The 18 infants whose ages are unknown all died.

It is significant that 10 of the 18 known recoveries took place since 1939, when the sulfonamide drugs came into general use. Prior to that time the treatment was symptomatic and supportive, with occasional spinal drainage and administration of antimeningococcus serum U.S.P. Of 128 patients treated in this manner, only 8, or 6 per cent, recovered. The remaining 19 patients received some sulfonamide drug (table 3), and of these, 10, or 52 per cent, recovered. Sulfadiazine was

the preparation used in the majority of these cases, including that of the 23 day old infant. There was no record of the use of a sulfonamide compound in any of the cases of newborn infants.

The prognosis is further influenced by the type of organism involved (table 2). Thus, recovery was noted in 9, or 41 per cent, of the 22 cases of meningitis due to S. paratyphi B; in 2, or 28 per cent, of the 7 cases of infection due to S. paratyphi A, and in 3, or 18 per cent, of 17 cases of infection due to S. panama. On the other hand, none of the 45 cases involving S. enteritidis and its varieties had a favorable outcome. If the patients treated with sulfonamide drugs are considered separately, the same situation is seen to prevail. Of the 4 patients with S. paratyphi B infections and the 4 with S. panama infections who were treated with a sulfonamide drug, 3 with each type of infection recovered, while the 2 patients with S. enteritidis infection who were treated with sulfonamide compounds died. High and Spalding,[71] in conducting in vitro tests for susceptibility with sulfonamide preparations on two strains of S. panama, discovered considerable variation in susceptibility, even among the strains of that one type, and they suggested that other strains would show much the same variation. They concluded that sulfadiazine and sulfathiazole were the drugs of choice among the sulfonamide compounds.

A few patients were treated with penicillin. In my case (2) in which meningitis was diagnosed only at autopsy, penicillin was used in treatment of the pneumonia. As would be expected, this antibiotic substance apparently has little effect on salmonella organisms. Streptomycin gives promise of being effective against infection with these organisms, but results to date are inconclusive. A limited amount was used for Barnes's[72] patient, who died after fifty-four days. Another patient treated with streptomycin[80] recovered.

Blood transfusion, although more of a supportive than a specific measure, should be mentioned. It is my belief, that in my first case it was as important as sulfadiazine in bringing about recovery. The use of transfusions was mentioned in 4 other cases in which recovery was noted.

Recovery may be marred by any of the residual changes seen in other types of purulent meningitis. Transient facial paralysis was noted in case 1. High and Spalding's patient[71] exhibited deafness, blindness, and partial paralysis. Valledor, García Pérez and Pedrera[65] mentioned mental changes in their patients, while several died with hydrocephalus after periods of apparent improvement and after cultures of the spinal fluid had become sterile.

At the beginning of the present paper it was mentioned that while 2 cases of salmonella meningitis were encountered in the Gorgas Hospital during 1946, only 1 case was found in a review of the hospital records for the previous twenty-one years. The discovery was surprising in view of the common occurrence of salmonella infections in this locality. However, it was noted in case 2 that meningitis was diagnosed only at autopsy. In case 3 the antemortem cultures of the spinal fluid showed no growth, and the etiologic agent would have remained unknown had not an autopsy been performed. It is likely, therefore, that a number of other cases have passed undiagnosed. Because of the many variable factors, it is impossible to calculate the incidence of salmonella meningitis, but it seems of frequent enough occurrence to merit consideration in any case of meningitis not readily identified as 1 of the commoner types.

SUMMARY

Three new cases of salmonella meningitis are added to 144 cases collected from the literature.

The characteristics of the disease are reviewed. It is seen to be the result of a septicemia, with locus minoris resistentiae an important factor. A certain few types of Salmonella account for the majority of the cases.

A combination of factors peculiar to newborn infants operates to make them especially susceptible to the infection. The clinical features for that group include an epidemic tendency, diarrhea and a rapidly fatal course, in contrast to sporadicity, common absence of diarrhea and better prognosis in older infants. In both groups, the course is febrile, with leukocytosis, while the spinal fluid shows an increase in number of cells, with an early predominance of neutrophils. The organism may often be seen on direct smear and is identified from cultural and serologic characteristics. At autopsy a purulent meningitis, with a tendency to basilar distribution of the exudate, is observed.

The course of the disease is favorably influenced by systematic treatment with sulfonamide compounds, sulfadiazine probably being the drug of choice. Of 19 patients treated in this manner, 10, or 52 per cent, recovered, while of 128 patients who did not receive a sulfonamide drug, only 8, or 6 per cent, recovered. Penicillin is ineffective. The usefulness of streptomycin remains to be investigated. Blood transfusion appears to be a valuable aid.

Prognosis further depends on the age of the patient and the type of organism causing the infection. Only 1 of 49 patients less than 1 month old recovered, whereas 17 of 80 children in the older age

group lived. Patients with infections due to S. paratyphi A, S. paratyphi B and S. panama accounted for the majority of those who recovered, while, of 45 persons with infections due to S. enteritidis and its varieties, all died.

Any of the sequelae typical of purulent meningitis may occur.

The disease is of common enough occurrence to warrant consideration whenever one is confronted with a purulent meningitis.

Carle Hospital Clinic.

SYSTEMIC ALEUKEMIC RETICULOENDOTHELIOSIS (LETTERER-SIWE DISEASE)

CHARLES VARGA, M.D.

MAURICE N. RICHTER, M.D.

AND

ADOLPH G. DeSANCTIS, M.D.

NEW YORK

RECENTLY, 3 cases of systemic aleukemic nonlipid reticuloendotheliosis were studied by us. The similarity of clinical course, and especially of the cutaneous lesions, prompted us to report them and to review the literature briefly.

The occurrence of reticuloendothelial disturbances has been known for many years.[1] Letterer [2] described a special type of reticuloendotheliosis in a young child almost twenty-five years ago. Nevertheless, relatively few of these cases have been reported.[3]

From the Department of Pediatrics and the Department of Pathology, New York Post-Graduate Medical School and Hospital.

1. Rowland, R. S.: Constitutional Disturbances of Lipid Metabolism, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1946, vol. 3, chap. 23, p. 18.

2. Letterer, E.: Aleukämische Retikulose, Frankfurt. Ztschr. f. Path. **30**: 377, 1924.

3. (*a*) Josephs, H. W.: The Anemias of Childhood, in Holt, L. E., and Howland, J.: Diseases of Infancy and Childhood, ed. 11, revised by L. E. Holt Jr. and R. McIntosh, New York, D. Appleton-Century Company, Inc., 1940, p. 627. (*b*) Rosenthal, N.: Letterer-Siwe's Disease, in Litchfield, H. R., and Dembo, L. H.: Therapeutics of Infancy and Childhood, Philadelphia, F. A. Davis Company, 1942, vol. 2, p. 1604. (*c*) Abt, A. F., and Denenholz, E. J.: Letterer-Siwe's Disease: Splenohepatomegaly Associated with Widespread Hyperplasia and Nonlipoid-Storing Macrophages, Am. J. Dis. Child. **51**:499 (March) 1936. (*d*) Siwe, S. A. Reticuloendotheliose—ein neues Krankheitsbild unter den Hepatosplenomegalien, Ztschr. f. Kinderh. **55**:212, 1933. (*e*) Wallgren, A.: Systemic Reticuloendothelial Granuloma: Nonlipoid Reticuloendotheliosis and Schüller-Christian Disease, Am. J. Dis. Child. **60**:471 (Sept.) 1940. (*f*) Dameshek, W.: Proliferative Diseases of the Reticulo-Endothelial System: Aleukemic Reticulosis, Folia haemat. **49**:64, 1933. (*g*) Wallgren, A.: A Case of Reticulo-Endotheliosis, Nord. med. (Nord. med. tidskr.) **15**:584, 1938. (*h*) Burckhardt, W.: Hand-Schüller-Christian Disease with Cutaneous Manifestations, Dermatologica **86**:250, 1942. (*i*) Foot, N. C., and Olcott, C. T.: Report of a Case of Non-Lipoid Histiocytosis, Am. J. Path. **10**: 81, 1934. (*j*) Letterer.[2]

REPORT OF CASES

CASE 1.[4]—A 5 month old white girl was admitted to the New York Post-Graduate Hospital on Aug. 13, 1946. The chief complaints included infected eczema, poor gain in weight, moderate diarrhea and drainage from both ears. She was a second child, weight at birth was 8 pounds 3 ounces (3,714 Gm.). There was no pertinent family history. Soon after birth papular, pustular and pyodermic lesions had been noted on the body and scalp. Occasionally, petechiae had been noted also. The organism cultured from the cutaneous lesions, a hemolytic Staphylococcus aureus, was resistant to sulfadiazine and penicillin (applied locally and given systemically), but susceptible to streptomycin. There was, however, little clinical response to a short course of streptomycin before her admission. Shortly before admission, generalized petechiae, bilateral purulent otitis media and slight hepatosplenomegaly developed.

On the patient's admission, the outstanding physical findings included a generalized pyodermic, seborrheic dermatitis, bilateral purulent otitis media, petechiae, moderate general lymphadenopathy and slight hepatosplenomegaly. Other systems showed no apparent involvement. Weight was 13 pounds 8 ounces (6,123 Gm.), temperature 101.4 F., pulse rate 110 and respirations 24. The cutaneous lesions were crusted and pustular, with some oozing of serous fluid from an erythematous base (plate).

The erythrocytes ranged from 5,759,000 per cubic millimeter of blood to 3,870,000; hemoglobin, from 13.8 Gm. per hundred cubic centimeters of blood to 10.3 Gm.; total leukocytes, from 12,200 per cubic millimeter of blood to 4,300; polymorphonuclear leukocytes, from 66 to 20 per cent; lymphocytes, from 21 to 73 per cent; monocytes, from 7 to 19 per cent, and platelets, from 190,000 to 250,000 (Rees and Ecker method). The Wassermann reaction was negative, and the tests with old tuberculin (in dilutions of 1:10,000 and 1:1,000) gave a negative reaction. Scrapings of skin were negative for fungi. Tests of the stool revealed no fat or starch. The urine was normal. Cultures of the blood and stool yielded no pathogenic organisms. The spinal fluid was normal. Blood cholesterol measured 100 mg. per hundred cubic centimeters. The vitamin A absorption test yielded normal values. Cultures of the skin and of material from the ear and mastoid revealed: (1) nonhemolytic streptococcus sensitive to penicillin, sulfonamide compounds and streptomycin and (2) hemolytic Staphylococcus aureus resistant to penicillin and sulfonamide compounds, but sensitive to streptomycin. In vitro, inhibition by streptomycin on August 22 was 16 micrograms per hundred cubic centimeters, and on September 20, 900 micrograms per hundred cubic centimeters.

In spite of treatment with sulfonamide compounds, streptomycin, various ointments, autogenous vaccine and transfusions, the cutaneous lesions and bilateral aural discharge improved and recurred several times. Diarrhea occurred on several occasions, but diagnostic study ruled out celiac disease. The temperature usually ranged from 99.5 to 101 F., with occasional elevations to 103 F. Because of recurrent purulent otitis media, simple mastoidectomy (bilateral) was performed. This operation effected no change in the condition. Since we suspected that we were dealing with a systemic disease, possibly reticuloendotheliosis, roentgenograms of the bones and biopsy specimens of the skin, lymph nodes and bone marrow were

4. This case history was first presented at the meeting of the Section on Pediatrics, New York Academy of Medicine, May 8, 1947.

obtained. The roentgenograms of bones revealed only moderate calcium deficiency in the cancellous portions of the long bones. The biopsies were partially confirmatory, but it was not until autopsy that definite diagnosis was established.

The child died on the one hundred twenty-fourth day in the hospital, after an acute febrile episode of five days' duration, during which numerous petechiae were seen.

Observations at Autopsy.—The principal gross observations, other than the cutaneous lesions mentioned previously, were enlargement of the spleen, liver and lymph nodes.

The spleen weighed 80 Gm., and it measured 13 by 8 by 5.5 cm. The organ was firm and deep purple. Prominent grayish spots suggesting malpighian corpuscles were seen on the cut surface.

The liver measured 19.5 by 12.5 by 6.5 cm. and weighed 435 Gm. The cut surface was light tan, and small yellowish areas in the lobules suggested accumulations of fat.

The enlargement of the lymph nodes was greatest in the cervical groups. Less pronounced enlargement was present in the axillary and inguinal groups, in the mesentery and in the nodes about the abdominal aorta.

The other organs showed no changes of interest. A mild pneumonic process associated with areas of atelectasis and emphysema was noted in the lungs.

Microscopically, the most important change was the presence in many organs of accumulations of mononuclear phagocytic cells with broad, granular, vacuolated cytoplasm, occasionally accompanied with multinucleated giant cells. Some of the cells, especially in the spleen, contained hemosiderin pigment.

In the spleen these accumulations often resembled small granulomas about the size of germinal centers. In addition, more diffuse collections of similar cells were in the splenic pulp. These accumulations were not associated with heterotopic formation of blood.

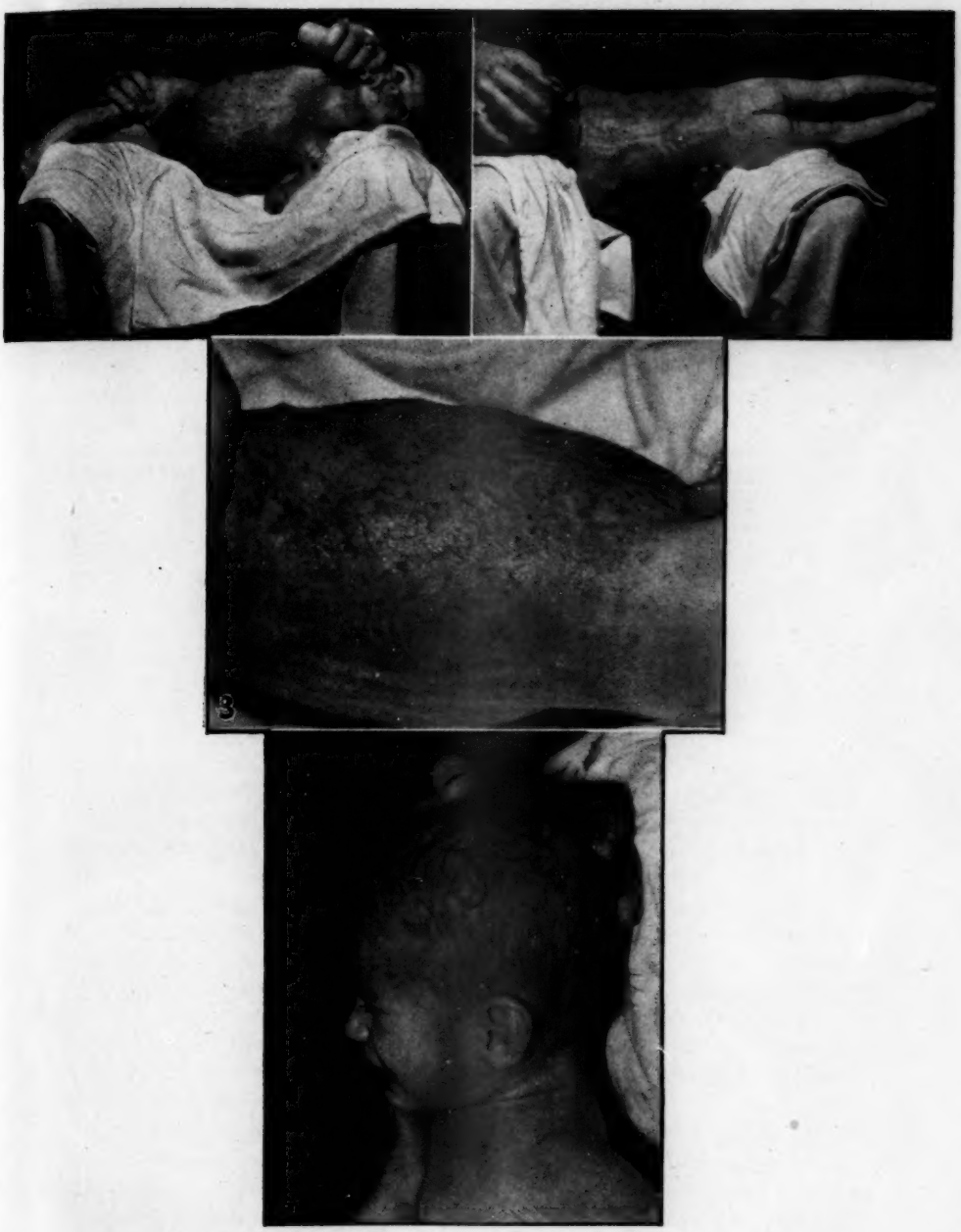
In the lymph nodes, similar cells were seen, especially in and near the sinuses. These cells resulted in enlargement of sinuses, which was associated with some reduction in numbers of lymphocytes. Germinal centers were small and inconspicuous, and in some nodes they were absent altogether. There was, however, no destruction of the underlying basic architecture of the nodes. The lymphoid tissues of the stomach, small and large intestine and vermiform appendix contained similar collections of cells.

The thymus gland had only a few cortical lymphocytes left, the rest being replaced with large numbers of mononuclear cells, some of which contained hemosiderin pigment. The bone marrow also had areas in which large numbers of cells of the same type replaced marrow cells.

Section of skin showed a thin zone of mononuclear cells immediately beneath the epithelium. The epithelium was thin, with irregular layers of keratin on the surface in some areas and absence of keratinized epithelium in others. The mononuclear cells did not extend into the underlying tissues.

These lesions in the specimen of skin removed for biopsy indicated extreme proliferation of reticulum cells. These changes, in association with proliferation of similar cells and the observation of occasional multinucleated giant cells on the biopsy of the lymph node, suggested the diagnosis of Letterer-Siwe disease.

The final diagnosis was: Nonlipid histiocytosis (Letterer-Siwe disease), with infiltration of skin, lungs, liver, bone marrow, spleen, kidneys, lymph nodes, thymus,



Photographs (case 1) showing cutaneous lesions. *1*, taken after crusts had been removed with soothing lotions and bland ointments, indicates the severe erythema and its distribution on the ventral surface. Although extremities are relatively uninvolved, shortly before death even the palms and soles were affected. *2*, similar picture of the dorsum. Absence of lesions in popliteal folds may be of some significance, for these areas are frequently involved in ordinary eczema. *3*, close-up view of the lesions in which the extreme irregularity of cutaneous surface with pitting due to denuded areas, scaling, crusting and some pustular areas are seen. *4*, pronounced involvement of the head and neck, with relatively little of the face. Erythema and crusting are evident. Some petechiae can be seen on the neck and in the frontotemporal area.

colon and appendix; splenomegaly; hepatomegaly; general lymphadenopathy; secondary anemia; petechial hemorrhages of skin, and bilateral chronic purulent otitis media.

CASE 2.—A 1 year old white girl was admitted to the New York Post-Graduate Hospital on March 27, 1946, with a history of recurrent fever (101 to 102 F.) for several months, spongy, bleeding gums and loose teeth, loss of weight and a cutaneous eruption. Petechiae were noted several times before admission. The family history was not contributory. Birth and the neonatal period were normal. She was a second child. Developmental history was slightly accelerated.

The outstanding physical findings on admission included bilateral purulent otitis media, hepatomegaly (with enlargement 3 fingerbreadths below the costal margin), extremely spongy hypertrophic gums, loose teeth, severe cervical lymphadenopathy and a cutaneous eruption. The lesions were vesicular, crusted, eczematoid and ulcerated, as well as petechial; they were noted on the scalp, the auricles of ears and the skin of the back, lower part of the abdomen, vulva, perianal areas and axilla. The lesions in the groin were moist and resembled so-called weeping eczema. There was evidence of pruritus. Scrapings of the skin showed no fungi. Cultures of the blood and urine yielded no pathogenic organisms. The reactions to the Wassermann and Mantoux tests were negative. Roentgenograms of bones showed no abnormality, and the Rumpel-Leede phenomenon was not present. Erythrocyte count ranged from 4,270,000 per cubic millimeter of blood to 2,240,000; leukocytes, from 10,700 per cubic millimeter of blood to 5,400; polymorphonuclear leukocytes, from 74 to 54 per cent; lymphocytes, from 37 to 19 per cent, and monocytes, from 3 to 7 per cent. Chemical studies of the blood revealed a normal ascorbic acid level (0.65 mg. per hundred cubic centimeters). Urea nitrogen measured 7.5 mg.; nonprotein nitrogen, 23.5 mg.; glucose, 45 mg.; calcium, 10.6 mg.; inorganic phosphate, 4.3 mg.; total protein, 6.2 Gm.; alkaline phosphatase, 15 units (Bodansky), and total cholesterol, 140 mg., per hundred cubic centimeters. The cephalin flocculation test showed a 1 plus reaction. Dextrose tolerance curves were normal. Culture of material from the discharging ear revealed Staphylococcus albus, hemolytic streptococci and Escherichia coli.

The course of the patient's illness became progressively worse in spite of treatment with antibiotic substances, multiple transfusions and large doses of vitamins. Anorexia developed. The temperature ranged from 99.5 to 103.5 F. She was released from our hospital on request of the parents. Shortly thereafter, however, the child was admitted to another hospital because of serious loss in weight, jaundice and apathy. Autopsy at that hospital revealed the presence of systemic nonlipid reticuloendotheliosis involving the skin, lymph nodes, spleen, liver, lungs, pancreas and large intestine.

CASE 3.—A 2 year old white girl was admitted to the New York Post-Graduate Hospital on May 24, 1939. The chief complaints included severe anorexia and loss of weight for one year. Birth and developmental history were normal. Family history was not contributory. At 9 months of age the child started having frequent colds and sore throat in addition to recurrent otitis media. A fracture of the right wrist developed at this age also. Although she gained weight normally during the first year of life, she started losing gradually during the second.

Physical examination on admission revealed a poorly nourished, white girl whose skin had a pale lemon hue. She appeared weak and irritable. The only other finding was that of moderate inguinal and axillary lymphadenopathy.

Results of laboratory examinations were as follows: red blood cell count range, from 3,850,000 per cubic millimeter of blood to 800,000; hemoglobin, from 12.2 Gm. per hundred cubic centimeters of blood to 2.6 Gm.; leukocytes, from 12,350 per cubic millimeter of blood to 4,150; polymorphonuclear leukocytes, from 19 to 54 per cent; lymphocytes, from 80 to 20 per cent; monocytes, from 1 to 4 per cent, and platelet count, from 105,000 to 62,000 cells. Sedimentation rate (Westergren) ranged from 127 to 143 mm. in an hour. The reaction to the Wassermann test was negative for syphilis. Agglutination series for heterophil antibodies gave negative results. Cultures of the blood yielded no pathogenic organisms. Cultures and examination of the stool revealed no ova or parasites. The reaction to the Mantoux test (in dilutions of 1:1,000 and 1:500, old tuberculin) was negative. The icterus index was 3.1. Total cholesterol measured 165 mg., cholesterol esters, 40 mg. and alkaline phosphatase, 3.9 Bodansky units, per hundred cubic centimeters. Bone marrow aspiration studies revealed no diagnostic features. Urinalyses revealed only a low specific gravity (1.001 to 1.006).

During her entire course in the hospital the child refused solid foods but accepted enriched fluids for which she seemed to crave. In spite of treatment with numerous blood transfusions, supplemental vitamins and iron and liver therapy, her course gradually went downhill. The desire for large amounts of fluids and the excretion of large amounts of dilute urine were noted during the tenth week in the hospital. Shortly prior to this time scattered petechiae and purpuric spots were noted on the abdomen. A few days later two small nodules were noted over the occipital region, and hepatomegaly was first observed. Several small nodules were palpable in the abdominal wall shortly before death. The temperature ranged from normal to 105 F., with usual daily rises to 103 F. Roentgenograms revealed proliferative periosteal changes with numerous small areas of rarefaction of the long bones and skull. A slight degree of lymphoid nodulation at the hilus with mottling of central pulmonary fields was also noted. The child died on the eighth day in the hospital.

Observations at Autopsy.—The gross observations of main interest were enlargement of lymph nodes in the cervical, inguinal and mesenteric groups and around the bifurcation of the trachea. The individual nodes varied in size, most of them being from 5 to 10 mm. in diameter. The spleen measured 9 by 6 by 4 cm. and weighed 80 Gm. On the cut surface, the follicular markings appeared to be exaggerated. The lungs were of normal size, but their pleural and cut surfaces were studded with numerous grayish nodules resembling miliary tubercles. The gross appearance of other organs was not of special interest.

Microscopically, miliary-sized granulomas were seen in the lungs, spleen, liver, lymph nodes, tonsils and the walls of the renal vessels in the peripelvic fat. In the bone marrow the lesions were more diffuse and were accompanied with fibrosis and formation of new bone along the finer trabeculae and in the periosteum. The dura mater in the region of the pituitary gland was involved in a similar process, which extended through the capsule of the gland to the superficial portion of the anterior lobe.

The miliary lesion consisted of accumulations of mononuclear cells with occasional giant cells, usually with a surrounding zone of lymphocytes and plasma cells. There was no necrosis. The cytoplasm of the mononuclear cells was finely granular, and many cells contained hemosiderin pigment, especially those in the splenic granulomas. In the lungs, many of the granulomas were adventitial and several were subintimal.

The more diffuse lesions consisted of larger areas with numerous mononuclear cells, many of "epithelioid" type, but they were not arranged in aggregates of special form. Among the mononuclear cells were a few multinucleated giant cells, not distributed in any recognizable relation to other structures.

The final diagnosis was nonlipid histiocytosis (Letterer-Siwe disease), with involvement of lymph nodes, spleen, bone marrow, renal pelves, lungs, liver, tonsils and dura mater.

COMMENT

The reticuloendothelial system is one which has been frequently discussed. Detailed information concerning its morphologic and physiologic features is readily available.[5] Several classifications of the various diseases of this group have been presented.[6]

In discussing rare diseases of bone, Mallory[7] stated that

> their multiple polysyllabic and still more confusing eponymic terminologies constitute the most perplexing field in medicine, a field so esoteric that it is apt to be relegated far back into the realms of the subconscious (of most physicians).

Certainly, the statement is equally applicable to the reticuloendothelial diseases. The relation of xanthomatoses,[7] leukemic reticuloendotheliosis,[8] aleukemic reticuloendotheliosis, mycosis fungoides,[9] Hodgkin's disease, monocytic leukemia,[9] reticulum cell sarcoma,[6c] eosinophilic granuloma of bone,[10] eosinophilic granuloma of skin[11] and the commoner granulomatous diseases remains to be clarified.

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5. (*a*) Robb-Smith, A. H. T.: The Reticular Tissue and the Skin, Brit. J. Dermat. **56**:151, 1944. (*b*) Jaffe, R. H.: The Reticulo-Endothelial System, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, pp. 973 and 1272. (*c*) Forbus, W.: Reaction to Injury: Pathology for Students of Disease Based on the Functional and Morphological Responses of Tissues to Injurious Agents, Baltimore, Williams & Wilkins Company, 1943, pp. 531-545.

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8. Becker, F. T.: Leukemic Reticuloendotheliosis, Arch. Dermat. & Syph. **39**: 378 (Feb.) 1939.

9. Wayson, J. T., and Weidman, F. D.: Aleukemic Reticulosis: Additional Member of Group of So-Called Cutaneous Lymphoblastomas, Arch. Dermat. & Syph. **34**:755 (Nov.) 1936.

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11. Weidman, F. D.: The "Eosinophilic Granuloma" of the Skin, Arch. Dermat. & Syph. **55**:155 (Feb.) 1947. Lewis, G. M., and Cormia, F. E.: Eosinophilic Granuloma: Theoretic and Practical Considerations Based on the Study of a Case, ibid. **55**:176 (Feb.) 1947. Lever, W. F.: Eosinophilic Granuloma of the Skin: Its Relation to Erythema Elevatum Diutinum and Eosinophilic Granuloma of Bone, ibid. **55**:194 (Feb.) 1947.

It appears from the literature that cutaneous lesions are an essential part of the picture of the disease. Although the lesions of Letterer-Siwe disease have generally been described as petechial or purpuric, it is of interest to note that lesions similar to and occasionally identical with those seen in our patients have been described in the literature.[12] Wallgren's description [3e] is most definitive—the cutaneous lesions

> at a cursory glance appeared to be seborrheic eczema . . . (They) consisted of sharply defined linear ridges and islands of slightly desquamated skin, separated by long and narrow furrows or more superficial, irregularly outlined areas of skin where the corium was exposed. Here and there were petechiae.

Various types of cutaneous lesions are frequently seen in the diseases associated with hyperplasia of the reticuloendothelial cells. Thus, patients with Schüller-Christian disease are reported [13] to have had pinhead-sized nodules with scales and purpuric spots on the chest, as well as seborrheic-like scales on the scalp. Localized tumors of various colors were reported.[14] Gangrenous lesions were also included.[3c] One realizes, therefore, that many solitary, as well as generalized, dermatologic lesions may represent a form of reticuloendotheliosis.

The criteria of Letterer-Siwe disease were listed as follows:[15]

1. Marked splenomegaly is present with moderate to considerable enlargement of the liver.
2. A hemorrhagic tendency, with petechiae or purpura, is noted.
3. A generalized glandular enlargement occurs, the nodes being discrete and nontender.
4. Localized tumors of bone (rarefactions) are seen. However, in 5 of 8 reported cases, no changes in bone were noted.
5. Secondary anemia, progressive and nonregenatory in type, may appear late in the disease, with normal or diminished white blood cells.

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12. Sweitzer, S. E.; Winer, L. H., and Cumming, H. A.: Reticuloendotheliosis, Arch. Dermat. & Syph. **40**:192 (Aug.) 1939. Letterer.[2] Wallgren (footnote 3*e* and *g*).

13. Stats, D., and Wassermann, L. R.: Lipoid Histiocytosis, in Hyman, H. T.: An Integrated Practice of Medicine: A Complete General Practice of Medicine from Differential Diagnosis by Presenting Symptoms to Specific Management of the Patient, Philadelphia, W. B. Saunders Company, 1946, vol. 2, p. 1134. Burckhardt.[3h]

14. Sweitzer, S. E.: Reticulo-Endotheliosis, Arch. Dermat. & Syph. **51**:278 (April) 1945. Twining, H. E.: Reticuloendotheliosis, ibid. **42**:748 (Oct.) 1940. Wayson and Weidman.[9]

15. Wallgren.[3e] Dameshek.[3f] Jaffe.[5b]

6. Moderate degree of fever is present in almost all cases.
7. The disease is neither hereditary nor of familial character.
8. Pathologic study reveals generalized hyperplasia of the reticuloendothelial system.
9. The onset is acute and unrelated to infections.

A review of the cases in the literature reveals, however, that many of them are associated with infections, especially otitis media and mastoiditis. This association, of course, does not imply an etiologic relation but merely emphasizes the need for eliminating one of the aforementioned original criteria. The duration of the disease in the reported cases was from three months to two and three-fourths years.

In consideration of the clinical diagnosis of a case on the aforementioned criteria, it has been pointed out that the last criterion is not a necessary one. The first seven criteria are not, in themselves, diagnostic because they may be observed in conditions other than Letterer-Siwe disease. If, however, pathologic examination reveals widespread proliferation of reticuloendothelial cells of the type described, the diagnosis is on more secure ground. Evidence of such hyperplasia may be obtained during life by histologic examination of lymph node, skin, bone marrow, splenic tissue and liver.

Although no attempt is made to indicate a therapeutic schema, it may be stated that two methods have been repeatedly considered, namely, the control of infection by antibiotic substances [16] and radiation. The antibiotic drugs effected no change in the progress of the disease in our cases. Radiation was not used because it is not generally considered effective and, in addition, a depression of the functional activity of the reticuloendothelial system by radiation with aggravation of existing infection has been noted. It has been stated that relative resistance of the reticuloendothelial cells to radiation may prove useful in the differentiation of the group of diseases in which they are involved from other diseases of the lymphatic system.[17]

The condition known as Letterer-Siwe disease may be less infrequent than supposed in the past. We have seen 3 cases in the past eight years at New York Post-Graduate Hospital. In addition, we know of 7 other cases in various hospitals in New York city during the past two years. The clinical similarity to commoner diseases, such as infantile eczema, and its pathologic similarity to many other granu-

16. Gellis, S. S.: Letterer-Siwe's Disease, in Nelson, W. E.: Textbook of Pediatrics (Mitchell-Nelson), Philadelphia, W. B. Saunders Company, 1945, p. 933.

17. Krumbhaar, E. B.: The Lymphomatoid Diseases (So-Called Lymphoblastomas), J. A. M. A. **106**:286 (Jan. 25) 1936.

lomatous diseases may have confused the diagnosis in the past. In general, dermatologists describe the cutaneous lesions as those occurring in infected eczema and clinically diagnose the lesions as such.

SUMMARY

Three cases of Letterer-Siwe disease (systemic aleukemic, nonlipid reticuloendotheliosis) are presented. Two of them exhibited cutaneous manifestations not unlike infected eczema. Emphasis is placed on the presence of these cutaneous lesions, as well as infections, especially purulent otitis media, in many of the reported cases. A brief discussion of the relation to many better known diseases is included. Difficulties in diagnosis and resistance to therapy are discussed.

303 East Twentieth Street (3).

EVALUATION OF CERTAIN PREPARATIONS FOR CARE OF THE SKIN OF NEWBORN INFANTS

M. A. PERLSTEIN, M.D.
CHICAGO

PROPER care of the skin of the newborn child, during its stay in the hospital nursery and after it reaches home, is an important problem in infant pediatrics. That there is little unanimity of opinion regarding such care seems largely due to a lack of understanding of the physiology and pharmacodynamics of the skin of the newborn and to the difficulty of apportioning the influence of nursing technic on conclusions otherwise reached.

Like other organs of the newborn, the skin differs from that of the adult both histologically and physiologically in many fundamental respects. The child's skin (after the vernix caseosa has been removed) is pink, soft and silken to the touch and exquisitely delicate in texture. Potter and Abel [1] reported that few babies display surface sterility at birth, the majority showing contamination, principally with Staphylococcus albus and Escherichia coli. After twelve to twenty-four hours, the skin becomes hyperemic, but the redness gradually fades by the end of the first week or ten days. This phase is often followed by a branny scaling or, less frequently, by desquamation in large plaques. The sebaceous glands are prominent, particularly on the nose, cheeks and chin, and may form tiny elevations known as milia. Since immunologic functions are poorly developed at this age, the integument of the newborn child is particularly susceptible to even minor irritations or infections, so that tissue changes may be disproportionate to the intensity of an excitant.

MILIARIA

In my experience, the commonest type of cutaneous condition seen in the nursery under average conditions (and hence chosen as a dermatologic index for purposes of this study) is miliaria rubra, or "prickly heat," known also as lichen tropicus, heat rash, red gum and strophulus.[2]

This study was aided by a grant from the Johnson Research Foundation.

From the Department of Pediatrics of the Belmont Community Hospital, Chicago.

1. Potter, R. T., and Abel, A. R.: Am. J. Obst. & Gynec. **31**:1003 (June) 1936.

2. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943.

Its importance lies in the frequency with which it leads to serious secondary infections, such as impetigo contagiosa, folliculitis and furunculosis, with devastating results in some cases.[3] The essential pathologic process in miliaria is an acute inflammation of the sweat glands, which appears suddenly and is characterized by the development of discrete, reddish, pinpoint-sized, elevated, round or conical papules, and miliary vesicles, or vesiculopapules.

The etiologic factor is not clear, but it has been suggested that excessive sweating is the essential cause. Although bacteria, generally staphylococci, are frequently recovered from the lesions, they are probably secondary invaders, since the secretions in early lesions are usually sterile. Excessive heat, humidity and clothing tend to aggravate the condition; hence, it is most commonly seen in the summer months. Anything that interferes with the evaporation of sweat, e. g., oils or greasy unguents, generally predisposes to an outbreak of miliaria.

Its pathogenesis probably entails some obstruction of the sweat ducts, with decreased sweat to the involved areas.[4] Mild inflammatory symptoms precede or follow and are characterized by local congestion and exudation and, in certain instances, by effusion of sweat about the ducts, resulting in a papular or a vesicular formation.[5] The sites most commonly affected are those of apposition of the skin, e. g., the neck, groin and axilla. However, the face, trunk or any other area may be involved, the palms and soles being affected least frequently.

The condition usually runs its course in two to ten days, the papules fading away and the vesicles drying into minute crusts. In some infants it may persist, varying in degree throughout the entire summer and reaching its peak during the hottest months. Even though its course is short, it tends to relapse if the cause is not eliminated, and new crops may prolong the eruption for weeks. In severe cases the vesicles coalesce to form bullous lesions, with increased susceptibility to secondary infection.

A variety of treatments, showing little regard to the physiologic concepts of prophylaxis, have been proposed, and there are advertised to members of the medical profession and the laity alike many preparations (with amazing numbers of ingredients) for use on the skin of newborn

3. McCandlish, H. S.: Am. J. Obst. & Gynec. **9**:228 (Feb.) 1925. Cole, H. N., and Ruh, H. O.: Pemphigoid of the New-Born (Pemphigus Neonatorum) with Report of an Epidemic, J. A. M. A. **63**:1159 (Oct. 3) 1914. Gandy, D. T.: Arch. Pediat. **52**:483 (July) 1935.

4. Sulzberger, M. B., and Zimmerman, H. S.: J. Invest. Dermat. **7**:61 (Feb.) 1946.

5. Tobias, N.: Essentials of Dermatology, ed. 2, Philadelphia, J. B. Lippincott Company, 1944, pp. 416-417. Wright, C. S.: Manual of Dermatology, Philadelphia, The Blakiston Company, 1940, pp. 37-38.

and older infants. Most of these preparations are not only pharmacodynamically ineffective but actually may aggravate the condition for which they are offered.

The present study was undertaken because of the importance of this problem and the fact that prior to the initiation of this investigation there was available no preparation or technic which would produce uniformly satisfactory results, except in the hands of persons highly trained in the care and handling of the newborn. The object of this investigation was to study certain preparations, developed on physiologic and bacteriologic concepts, for use on the skin of the newborn in the average general hospital nursery. The principles and data so acquired could then be projected into the field of home care of the baby, where the mother has little technical training and no elaborate facilities for the care of her infant.

METHOD OF STUDY

This investigation was conducted from April 1942 to May 1945, on 2,077 consecutive, newborn, full term infants. (No premature infants were included in this study.[6]) The entire study was carried out in the nursery of a one hundred bed general hospital in Chicago and employed a simple, well standardized technic, which was not varied in significant detail during the period of the study. The nursing technic follows:

Birth Room Technic.

1. The nurse scrubs her hands before handling the baby.

2. Hand prints of the baby are taken.

3. The hands of the baby are cleansed of ink with mild soap and water.

4. The head is washed of blood and exudate with mild soap. The excess vernix is removed with a sterile sheet in the crib. Starting at the head and proceeding to the extremities, the trunk and, finally, the buttocks, the nurse freely anoints the baby with an ointment containing 1 per cent ammoniated mercury in a water-miscible base, or with the preparation under investigation. This ointment is applied to the skin with the nurse's hands.

5. The baby is wrapped in a blanket and its taken to the nursery, where he he is weighed, dressed and put into the crib.

Nursery Technic.

1. On admittance to the nursery, the infant is dressed in sterile clothing, and the receiving blanket from the delivery room is discarded.

2. On the first day, the newborn infant receives no bath in the nursery because he has already been cleansed and the skin has been cared for in the delivery room.

3. On the second day, the infant receives a sponge bath with tap water and a mild soap.

4. On the third, fifth, seventh and ninth days, the preparation under investigation is applied to the skin.[7]

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6. Description of a new method for clinical evaluation of technics for care of the skin made on premature infants will be reported separately.

(Footnotes continued on next page)

The General Inunction.—(*a*) From an individual bottle, the nurse pours a small amount of the substance under investigation into her palm and applies it to the baby's face, scalp, ears and neck and behind the ears. As cotton apparently absorbs the lotion, use of the bare hand seemed more satisfactory and faster. (*b*) The inunction is applied to the chest, axillas, arms, hands and abdomen. (*c*) The baby is turned and the inunction applied to the back. (*d*) The baby is again turned and the inunction is applied to the legs and feet.

5. The baby is then dressed on the table with clean, sterilized clothing and returned to bed. The bedclothing is changed daily while babies are out for breast feedings and whenever otherwise indicated. The nurse washes her hands between the handling of each baby and/or after using the pencil attached to the chart, adjusting the window shade, picking up something from the floor or performing other acts which might result in contamination of the hands.

The baby's skin was examined daily, and the various lesions observed were recorded on a special card. Many other eruptions, such as impetigo, "flea bite" dermatitis, seborrhea, excoriations and fissures, were observed. As noted earlier, however, the incidence of miliaria was employed as an index of the efficiency of a given preparation because it occurred most frequently, was most easily recognized and was often the precursor of more serious cutaneous conditions, e. g., impetigo.

CLINICAL OBSERVATIONS

At the start of the study, groups of 5 babies were alternated, the first group receiving the previously established technic (rubs [8] with ammoniated mercury ointment U.S.P., 1 per cent,[9] on the first and fifth days and with a bland, lubricant, water-miscible skin oil on other days); the second group received "antiseptic" oil J daily.[10]

In April 1942, about one week after the start of the study, a mild outbreak of impetigo occurred. A nurse in the nursery had a paronychia. Impetigo developed in 6 babies; 3 were receiving the rubs with ammoniated mercury and 3, rubs with "antiseptic" oil J. All 6 infants had mild impetigo, consisting of only three or four lesions, mostly in the region of the neck. The condition was easily controlled and subsided quickly.

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7. Applications every other day, instead of daily, entailed less handling of the baby (daily applications were deemed unnecessary) and reduced the opportunity for secondary infection of the skin. During several periods, however, daily applications were employed. These periods are indicated in their appropriate sequence.

8. Chadwell, O. R.: New England J. Med. **199**:983 (Nov. 15) 1928.

9. Ammoniated mercury, 1 per cent, in a water-miscible base containing 6 per cent oxycholesterol in petrolatum, was considered as good an antiseptic as a 2 per cent strength in petrolatum. The water-miscible base not only allows a greater concentration of the drug to come into actual contact with the skin, but also permits better cutaneous evaporation (and less miliaria) than petrolatum.

10. This preparation is a medicinal grade liquid petrolatum U.S.P., containing a small amount of hydrous wool fat U.S.P. and 8-hydroxyquinoline, as an antiseptic agent.

Early in the investigation, it was thought unwise to eliminate entirely the rubs with ammoniated mercury ointment, although it has been stated that medicated oil used alone has greater inhibiting powers on surface bacterial growth than when used with ammoniated mercury ointment.[1] Therefore, the routine for May and part of June 1942 employed a rub with ammoniated mercury ointment on the first day, followed by rubs with "antiseptic" oil J on subsequent days. In June, however, the initial ammoniated mercury rub was eliminated, and "antiseptic" oil J alone served as a daily inunction thereafter. Thirty-five infants received ammoniated mercury rubs only and 48 the combined technic, prior to July 1942.

In fourteen months prior to June 1943, 802 infants received "antiseptic" oil J only. Three cases of pustular lesions were seen during this period, and they occurred in the warm months of August and September 1942, a time when impetigo was rife in many Chicago nurseries. (Concomitantly, there occurred minor epidemics of diarrhea of the newborn in several Chicago nurseries, necessitating the closure of one. The 3 infants with impetigo were delivered by physicians who also attended the hospital in which the nursery was later closed.) In none of the infants was the impetigo severe; none exhibited more than two or three lesions; no secondary cases occurred; in all 3 the disease cleared rapidly under treatment with 5 per cent sulfathiazole ointment. Among this entire group, an occasional case of mild cutaneous irritation, such as intertrigo or seborrhea, was observed, but no irritation, other than the miliaria, could be attributed to the use of the "antiseptic" oil.

In the succeeding two years attention was directed to comparative evaluation of various lotions. My interest in preparations of this nature arose from independent studies of the physiology of infants' skin, which will be reported elsewhere. In these studies it appeared likely that oily preparations, by covering the skin with a continuous, impervious, multimolecular film, might interfere with important functions, such as respiration and elimination, and thus predispose, among other things, to miliaria. The three types of lotion studied consisted of a water in oil emulsion, designated as BL 18,[11] and two oil in water emulsions, designated as 10 F [12] and 10 FA,[13] respectively.

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11. The preparation is a dispersion of water in a mixture of a medicinal grade liquid petrolatum U.S.P. and hydrous wool fat U.S.P., utilizing bland, nonhydrolyzing, emulsifying agents.

12. This lotion is an oil in water emulsion of medicinal grade liquid petrolatum U.S.P. and hydrous wool fat U.S.P., stabilized with a bland, nonhydrolyzing, emulsifying agent and homogenized to extremely fine particle size.

13. The preparation is identical with lotion 10 F, with the addition of a small amount of 8-hydroxyquinoline as an antiseptic agent. This preparation is available commercially.

During June and July 1943, 137 babies were given daily rubs with lotion BL 18; in addition, because this contained no antiseptic, 1 per cent ammoniated mercury in oxycholesterol-petrolatum ointment base ("aquaphor") was employed as a rub on the first and fifth days. Twenty-six of these babes exhibited some degree of miliaria.

During August, September and October 1943, 227 babies received daily applications of lotion 10 F, together with 1 per cent ammoniated mercury in oxycholesterol-petrolatum ointment base on their first and fifth days. In this group, 16 cases of miliaria and 1 of impetigo occurred. The impetigo appeared in October and cleared rapidly under treatment with 5 per cent sulfathiazole ointment.

From November 1943 to the completion of the study, with the exception of three periods to be mentioned, lotion 10 FA was employed exclusively. One of the exceptions occurred from March 15 through April 15, when a baby oil [14] was employed because the lotion was temporarily unavailable. Coincidentally, miliaria increased from 1 to 3 per cent, in the months immediately preceding, to 16 per cent and dropped promptly with return to use of lotion 10 FA, even though it was then early summer.

On Nov. 28, 1944, the supply of lotion 10 FA was exhausted and was not resplenished until December 4. During this period another "antiseptic" oil ("antiseptic" oil M [15]), similar to that used in 1942 and 1943, was substituted. During this seven day period the incidence of miliaria increased markedly, exceeding even that usually seen during hot summer months. (The increase appears in the figures for December, since data were compiled according to date of discharge.)

Again, from April 23 until May 5, the lotion was temporarily unavailable, and "antiseptic" oil M was substituted once more. As before, the incidence of miliaria increased, 5 cases appearing in the twelve day period, approximately a 50 per cent increase in incidence. Most significant, however, was the simultaneous occurrence of 5 cases of impetigo, the first outbreak since 1942. (This outbreak was coincident with an epidemic of impetigo in many Chicago nurseries.) After these cases were controlled and the use of lotion 10 FA was resumed, no new miliaria or impetigo was seen.

COMMENT

In evaluating the data, a well marked seasonal variation in the occurrence of miliaria and of other cutaneous conditions, e. g., impetigo, should be noted. In my experience during hot summer months, the frequency

14. This preparation, designated as plain oil J, was a commercially available bland baby oil containing no antiseptic.

15. This preparation is a mixture of vegetable oils and liquid petrolatum U.S.P., containing hydroquinone, chlorobutanol and 8-hydroxyquinoline.

of miliaria has reached 50 per cent in untreated groups of newborn infants. Similarly, the case rate for impetigo tends to increase during the summer (when miliaria is rife), under conditions of overcrowding and inadequate nursing technic, and during spasmodic epidemics, such as were observed in the course of this investigation.

The graph demonstrates the incidence of miliaria relative to the number of newborn infants studied each month and reflects the effect of various preparations, as well as that of normal seasonal variation, on case rate. The area between the line for incidence of miliaria and that for nursery census demonstrates the relative efficacy of the preparation under investigation. As noted before, the graph exhibits an inherent time lag,

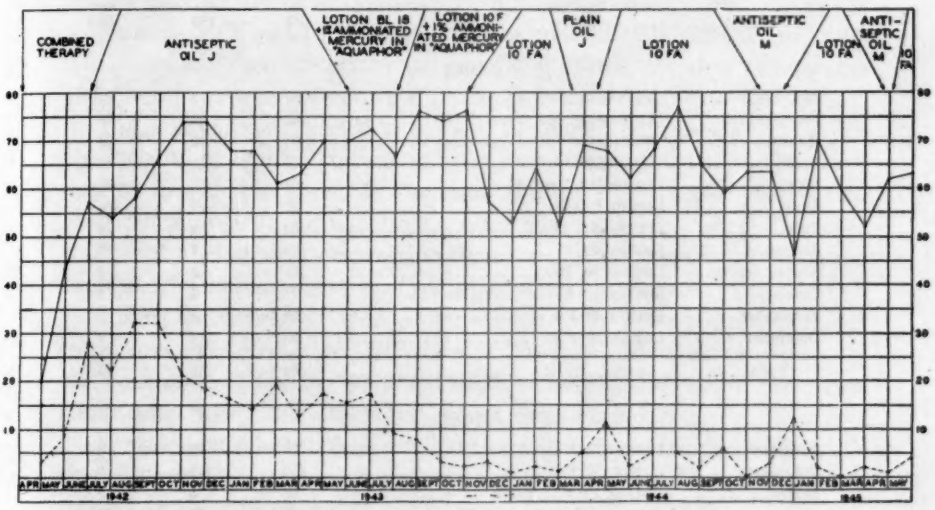

Chart showing the effect on the incidence of miliaria of experimental application of medicaments in relation to infant admissions. The solid line shows the number of infants admitted to the study, and the broken line shows the case incidence of miliaria.

data being compiled by date of discharge, so that changes occurring in November may appear under December, since some infants admitted in November were discharged in December.

The table summarizes the data for the entire thirty-eight month study and supplements the graph. In the table, the incidence of miliaria relative to the number of nursery admissions is clearly shown. With allowance for the influence of seasonal variation, the apparent, relative efficacy of the various preparations for preventing miliaria is also shown.

The greatest number of eruptions occurred during the period of the use of "antiseptic" oils. Experience in this study would indicate that oil constitutes an effective emollient for the skin, but that, however "anti-

Summary of Data Gathered in Study of Preparations for Cleansing of Skin of the Newborn

Month	Preparation	Number of Babies in Nursery	Cases of Miliaria	
			Number	Per Cent
1942				
January	.....	..	..	..
February	.....	..	..	..
March	.....	..	..	..
April	"Antiseptic" oil J	20	3	15
May	"Antiseptic" oil J	44	8	19
June	"Antiseptic" oil J	57	28	50
July	"Antiseptic" oil J	54	22	41
August	"Antiseptic" oil J	58	32	55
September	"Antiseptic" oil J	67	32	48
October	"Antiseptic" oil J	74	21	28
November	"Antiseptic" oil J	74	18	25
December	"Antiseptic" oil J	68	16	23
Total		516	180	34.8
1943				
January	"Antiseptic" oil J	68	14	20
February	"Antiseptic" oil J	61	19	31
March	"Antiseptic" oil J	63	12	19
April	"Antiseptic" oil J	70	17	24
May	"Antiseptic" oil J	68	15	23
June	Lotion BL 18	71	17	24
July	Lotion BL 18	66	9	14
August	Lotion 10 F	76	7	10
September	Lotion 10 F	74	3	5
October	Lotion 10 F	77	2	2
November	Lotion 10 FA	57	3	5
December	Lotion 10 FA	53	1	2
Total		804	119	14.8
1944				
January	Lotion 10 FA	62	2	3
February	Lotion 10 FA	55	1	2
March	Lotion 10 FA; plain oil J	69	5	7
April	Plain oil J; lotion 10 FA	68	11	16
May	Lotion 10 FA	62	2	3
June	Lotion 10 FA	68	5	8
July	Lotion 10 FA	77	5	6
August	Lotion 10 FA	65	2	3
September	Lotion 10 FA	59	6	10
October	Lotion 10 FA	63	0	0
November	Lotion 10 FA; "antiseptic" oil M	63	3	4
December	"Antiseptic" oil M; lotion 10 FA	46	12	26
Total		757	54	7.1
1945				
January	Lotion 10 FA	70	2	3
February	Lotion 10 FA	59	0	0
March	Lotion 10 FA	52	2	4
April	Lotion 10 FA; "antiseptic" oil M	62	1	2
May	"Antiseptic" oil M; lotion 10 FA	63	4	6
Total		306	9	3

septic," it will not prevent or control impetigo. It was generally true that the epidemic of impetigo was anticipated by the increase in miliaria enhancing the susceptibility to infection.

Emphasizing the superiority of the lotions was the sharp drop in incidence of miliaria even in summer, when an increase ordinarily is anticipated. Almost 50 per cent of babies in this nursery had miliaria in the warm months when oil was used. With the switch to the lotions the incidence dropped to less than 10 per cent. The improvement in the cutaneous condition with the use of the lotion type of preparations was dramatic and seemed entirely attributable to their use. That the drop during the winter months in which the use of lotion was initiated was not due solely to colder weather is indicated by failure of the rate of incidence to rise in the summer months that followed.

Lotions 10 F and 10 FA appeared pharmaceutically superior to lotion BL 18, which often thickened and separated into layers after autoclaving and, therefore, was not subjected to further trial.

For comparison, note that 8 cases of impetigo occurred during the six months in which "antiseptic" oil J was employed; 1, in the three months in which lotion 10 F was used, and none, in the two year period in which lotions BL 18 and 10 FA were administered. These data corroborated the clinical impression that in the prevention of impetigo avoidance of miliaria is at least as important as antisepsis.

Infant skins treated with either of the lotions were smoother and softer and exhibited fewer irritative rashes than did those on which oil had been used. (The nurses noted improvement in the skin of their own hands when using the lotions for even a short period.)

It also should be emphasized that the reduction in incidence of irritation and infections of the infants' skin occurred in spite of frequent understaffing and overcrowding of the nursery.

CONCLUSIONS

Of all the preparations studied in this investigation, water in oil emulsions, typified by lotions 10 F and 10 FA, appear to be the most effective, as judged by their ability to maintain at a minimum the incidence of irritation, impetigo and miliaria.

From a physiologic standpoint, an important advantage accrues from their inherent discontinuous, but protective, film which does not interfere to any significant degree with the metabolic and respiratory functions of the skin.

The particular value in the prevention of miliaria or impetigo is attributed to the character of the vehicle in lotion 10 FA, rather than to the antiseptic it contains. Comparison of lotion 10 F and lotion 10 FA would indicate that the antiseptic (8-hydroxyquinoline) in the latter is not an irritant.

An incidental observation was that preparations of the lotion type, particularly 10 F and 10 FA, exerted a decided mechanical cleansing action, desirable and convenient in removing particulate matter from creases of the skin and other intertriginous areas.

The use of preparations consisting principally of liquid petrolatum U.S.P. is not desirable because of irritation produced by the "smothering" effect of the oil, which interferes with the processes of respiration and loss of moisture. These observations afforded no basis for confirming the statement of Potter and Abel [1] that "it is probable that oil, in itself, has a beneficial effect on the skin and increases its resistance to infection." However, the amount and physical characteristics of the oil in the lotions studied did not appear to interfere with the physiologic functions and supplied a desirable degree of lubrication and protection from extraneous irritants such as urine and clothing.

There exist many different opinions as to the most effective treatment of the skin of the newborn; they range from the "do nothing" school to the use of a variety of preparations and technics with little objective substantiation. It is undoubtedly true, however, that skilful technic in a specially trained nursing staff is in itself the most important single factor in lowering the incidence of cutaneous infection in the newborn.

SUMMARY

The efficacy of various types of preparations for the infant skin in the prevention of irritation, miliaria, impetigo contagiosa and associated cutaneous disorders was studied in 2,077 newborn, full term infants.

During the course of this study, the case incidence of miliaria was reduced from 55 per cent, in August 1942, to 3 per cent, in August 1945.

This remarkable reduction in the occurrence of miliaria appeared to be due to the use of an oil in water emulsion, the content and construction of which are described.

This preparation, when used according to the methods outlined, is eminently satisfactory for prophylactic care of the newborn infant's skin, under conditions pertaining to the average nursery or home.

185 North Wabash Avenue (1).

Case Reports

RECURRENT POLIOMYELITIS

MAX J. FOX, M.D.; WILLIAM J. MADDEN, M.D.
AND
SAMUEL E. KOHN, M.D.
MILWAUKEE

FROM 1921 to 1946, 1,108 cases of acute poliomyelitis were diagnosed and the patients treated at the South View Hospital of the Milwaukee Health Department. Of these cases, death occurred in 102.

In August 1946, an 8 year old boy was admitted to the hospital with a diagnosis of acute bulbar poliomyelitis. His past history showed a period of hospitalization at South View Hospital one year previously for acute spinal poliomyelitis. We wish to add this case to the medical literature as an instance of recurrence in this disease. The literature includes reports of 35 cases of recurrent poliomyelitis. A review of these cases shows that approximately 45 per cent have been considered doubtful.

Of the cases listed in the table, several were considered doubtful by many authors. The cases of Caudouin,[1] Harmon [2] and Neal and associates [3] were discarded as lacking details necessary for the diagnosis; Cohen's case [4] was questioned because of the lapse between the time of the attack of paralysis (September 1933) and the time that Cohen first saw the patient (January 1944). The cases of Moore [5] and Quigley [6] were doubtful because of preceding infections with measles and bronchopneumonia. Sanz's case [7] was rejected by many authors because he saw the patient twenty years after the second attack and could not eliminate the possibility of the presence of a toxic form of neuritis. Toomey [8] called Taylor's [9] case one of probable toxic neuritis. In Francis and Moncreiff's [10] case there was a history of rhinopharyngitis, with reinfection occurring in February, out of the

From the South View Hospital of the Milwaukee Health Department and the Department of Internal Medicine, Marquette University School of Medicine.

1. Caudouin: Thesis, Paris, 1879, cited by Still.[18]

2. Harmon, P. H.: Personal communication, cited by Fischer and Stillerman.[18]

3. Neal, J. B., and others: Personal communication, cited by Fischer and Stillerman.[18]

4. Cohen, L.: New England J. Med. **213**:601, 1935.

5. Moore, T.: Brit. M. J. **2**:166, 1934.

6. Quigley, T. B.: Second Attacks of Poliomyelitis: Review of the Literature and Report of a Case, J. A. M. A. **102**:752 (March 10) 1934.

7. Sanz, F.: Siglo méd. **62**:530, 1915.

8. Toomey, J. A.: Second Attacks of Poliomyelitis, Am. J. Dis. Child. **56**:969 (Nov.) 1938; J. Immunol. **35**:1, 1938.

9. Taylor, E. W.: J. Nerv. & Ment. Dis. **44**:207, 1916.

10. Francis, F. D., and Moncreiff, W. F.: J. Nerv. & Ment. Dis. **49**:273, 1919.

Case No.	Author	Dates of Attacks	Interval Between Attacks, Yr.	Parts Affected
1	Eshner [11] *	1891 1903	12	1. Right lower extremity 2. Weakness in both hands (followed injury)
2	Eckert: Deutsche med. Wchnschr. **37**:113, 1911	1903 1909	6	1. Left leg 2. Right leg
3	Sheppard [12] *	1894 1910	16	1. Lower extremities 2. Hands, abdomen, lower extremities, acute ascending myelitis (Landry's paralysis)
4	Lucas and Osgood [19]	1910 1912	2	1. Both feet, right leg 2. Right arm, both legs
5	Oulmont, E., and Baudoin, A.: Rev. neurol. **21**: 333, 1911*	1911 1912	1	1. Flaccid paralysis of arms and legs, with recovery 2. Flaccid paralysis of arms and legs, followed by death
6	Taylor [9] *	1911 1914	3	1. Right leg, left arm 2. Left leg
7	Neal and others [3]	1907 1916	9	1. Left arm 2. No paralysis
8	Francis and Moncreiff [10] *	1903 1918	15	1. Upper extremities 2. Lower extremities
9	du Busc, L. C. V.: Personal communication, cited by Fischer and Stillerman [13]	1916 1922	6	1. Right leg 2. Left leg
10	Neal [3]	1903 1923	20	1. Both legs 2. Left thigh
11	Nelson and Green [17]	1923 1928	5	1. Legs, abdomen, back 2. Abdomen, back
12	Still [18]	1924 1929	5	1. Left leg 2. Right shoulder
13	Tesdal, M.: Norsk mag. f. laegevidensk. **95**: 978, 1934	1905 1929	24	1. Both legs 2. Both arms
14	du Busc, L. C. V.: Personal communication, cited by Fischer and Stillerman [13]	1923 1931	8	1. Both legs 2. Bulbar type
15	Nelson and Green [17]	1927 1931	4	1. Left leg 2. Bulbar type
16	Cohen [4] *	1908 1933	25	1. Right arm, right leg 2. Left arm, right leg
17	Moore [5] *	1927 1933	6	1. Lower extremities 2. Hands, abdomen, lower extremities
18	Nelson and Green [17]	1931 1933	2	1. Both arms 2. Both legs
19	Quigley [6] *	1931 1933	2	1. Left shoulder 2. Bulbospinal type
20	Toomey [8] *	1916 1933	17	1. Lower extremities 2. Upper and lower extremities
21	Tesdal, M.: Norsk. mag. f. laegevidensk. **95**: 978, 1934	1916 1934	18	1. Right arm, lower extremities 2. Arms, legs, trunk
22	Casaubon, A., and Cossoy, S.: Semana méd. **2**: 1201, 1935	1933 1935	2	1. Upper and lower limbs 2. Upper and lower limbs
23	Fischer and Stillerman [13]	1930 1935	5	1. Right shoulder, right leg 2. Left external rectus muscle, and right thigh
24	Fischer and Stillerman [13]	1931 1935	4	1. Right lower extremity 2. Nonparalytic
25	Fischer and Stillerman [13]	1931 1935	4	1. No paralysis 2. Bulbar type, right upper extremity; patient died
26	Fischer and Stillerman [13]	1933 1935	2	1. Right leg 2. Right leg and thigh, left thigh, upper part of abdomen

Data on Cases of Recurrent Poliomyelitis—Continued

Case No.	Author	Dates of Attacks	Interval Between Attacks, Yr.	Parts Affected
27	Nelson and Green [17]	1927 1935	8	1. Left leg 2. Left arm
28	Bolzinger, R., and Falconnet, R.: Soc. de méd. mil. franç., Bull. mens. **30**: 83, 1936	1922 1936	14	1. Not given 2. Total paralysis of one extremity and paresis of the other
29	Nielson, O. J.: Hospitalstid. **81**: 333, 1938	1908 1938	29	Not stated
30	Fox, Madden and Kohn, present case	1945 1946	1	1. Spinal type 2. Bulbar type
31	Ballet and Dutil [14] *	Not stated	9 2	1. Left leg 2. Upper extremities 3. Lower extremities
32	Caudouin [1] *	Not stated	14	1. Left leg 2. Right leg
33	Harmon, P. H.[2] *	Not stated	8	1. Both legs 2. Both legs
34	Harmon, P. H.[2] *	Not stated	17	1. One leg 2. One arm, both legs
35	Peremans [15] *	Not stated	2	1. Left leg 2. Left arm
36	Sanz [7] *	Not stated	14	1. Left leg 2. Right leg

* Listed as doubtful cases.

season for poliomyelitis. Eshner [11] himself regarded the nature of the second attack in his case as doubtful, a situation that obtains in Toomey's case [8] also.

Quigley's [6] article excluded the cases of Sheppard [12] and Eshner [11] because the diagnosis of one or both attacks was obscured by insufficient data, concomitant disease or trauma. Fischer and Stillerman [13] listed as doubtful the cases of Eshner,[11] Caudouin,[1] Ballet and Dutil,[14] Peremans,[15] Moore [5] and Harmon.[2] A discrepancy can readily be seen between the number of cases reported as second attacks and the number accepted as such.

In addition to the cases recorded in the literature, there are undoubtedly many that have escaped recognition or that have not been reported. Kramer, in a personal communication to Fischer and Stillerman [13] claimed to recall 6 or 7 cases of second attacks, but he furnished no details. Many authors stressed the importance of compiling more information regarding the immunologic factors, recrudescence and recurrence of acute poliomyelitis.

In 1946, a patient with recurrent poliomyelitis was observed for the first time by the Milwaukee Health Department.

11. Eshner, A. A.: M. Rec. **78**:526, 1910.

12. Sheppard, P. A. E.: West. M. Times **36**:93, 1916-1917.

13. Fischer, A. E., and Stillerman, M.: Does an Attack of Acute Anterior Poliomyelitis Confer Adequate Immunity? Report of Four Second Attacks in New York City in 1935, J. A. M. A. **110**:569 (Feb. 19) 1938.

14. Ballet, G., and Dutil, A.: Rev. de méd. Paris **4**:18, 1884.

15. Peremans, G.: Scalpel **76**:1319, 1923.

REPORT OF CASE

First Episode.—J. V., a white boy 7 years of age, was admitted to South View Hospital on Aug. 1, 1945, an epidemic year for poliomyelitis in the city of Milwaukee. His complaints on entrance were fever, headache, vomiting and stiffness of the neck and back. The symptoms dated back to July 23, with the stiffness of the neck and back occurring two days before his entrance to the hospital.

Physical examination revealed the child to be well nourished and well developed. Confirmatory observations were nuchal rigidity, spasm of the muscles of the lower part of the back, including the glutei, and bilateral spasm of the hamstring muscles. The Kernig and Brudzinski signs were positive, and the tendon reflexes were hyperactive. There were no tremors, twitching or paralyses, but pain with motion of the lower part of the back, as well as in the calf muscles, was apparent. The patient was unable to get into a sitting position from the supine one without pulling himself up manually, and he could not sit erect unless he supported his body with his hands behind him. There were no symptoms of bulbar involvement.

A lumbar puncture was performed, and 5 cc. of clear fluid was withdrawn, under normal pressure, for diagnostic purposes. There were 78 cells per cubic millimeter, mostly lymphocytes. The chlorides measured 684 mg., dextrose 59 mg. and total protein 20 mg., per hundred cubic centimeters, with no increase in globulin. The blood showed 5,600,000 red cells and 16,500 white cells per cubic millimeter, with a normal differential count.

The condition was diagnosed as acute anterior spinal poliomyelitis.

The patient was given hot fomentations three times a day during his sixteen day stay in the hospital, and he was then discharged to the Milwaukee Children's Hospital for further convalescent care. From there he was sent home, where he received hot packs for three months. No residual paralysis resulted.

Second Attack.—The patient was next seen at the Milwaukee Children's Hospital on the evening of Aug. 6, 1946. He complained of pain in the back of his neck of two days' duration, accompanied with fever, vomiting, inability to swallow solid foods or liquids without nasal regurgitation, nasal phonation, inability to cough and diplopia.

Physical examination revealed the 8 year old child to be thin and apprehensive. The muscles of the neck were spastic on attempted flexion, causing the patient much pain. The eyes were clear and reacted to light; but the pupils were small, and diplopia was elicited. The tongue protruded to the left, and there was paralysis of the soft palate, with deviation of the uvula. The deglutition reflex was decreased, and the cough reflex was not elicited. Slight spasm of the muscles of the back and the hamstring muscles was present, and the Kernig and Brudzinski signs were present. The patellar reflexes were exaggerated, while the abdominal and cremasteric muscle reflexes were sluggish.

A spinal puncture was performed, and 5 cc. of clear fluid was withdrawn under normal pressure. Examination of the fluid revealed 32 cells per cubic millimeter, all lymphocytes, with normal values for protein, chlorides and dextrose and no change in the colloidal gold curve. The blood showed 15,400 leukocytes per cubic millimeter, with 73 per cent neutrophils, 1 per cent eosinophils, 3 per cent basophils, 5 per cent monocytes and 18 per cent small lymphocytes. There were 6,050,000 red blood cells, with 17.5 Gm. of hemoglobin per hundred cubic centimeters. The sedimentation rate was normal.

The condition was diagnosed as bulbospinal poliomyelitis, and this diagnosis was confirmed when the patient entered South View Hospital on August 7. He was given 30,000 units of penicillin every four hours during his first four

days in the hospital as a prophylactic measure against secondary infection. Hot fomentations were placed on the neck, back and extremities twice daily. He was given a soft diet and received other routine care during his fourteen day stay in the hospital, after which he was transferred to the Milwaukee Children's Hospital for further convalescent therapy.

INCIDENCE

There are few illustrations of recurrence in this disease. Fischer and Stillerman [15] estimated that their rate of 2 per thousand cases was within the limits of expectancy of second attacks if no immunity developed from the previous attack. They based this rate on the observations of Phelps,[16] who estimated the upper limit of statistical significance as 1.5 previous attacks per thousand new cases, determined from the incidence of the disease over a twenty year span. Nelson and Green [17] showed a rate of 0.66 per thousand cases in their series at the Harvard Infantile Paralysis Commission. South View Hospital's rate of second attacks of poliomyelitis is 1 in 1,108 cases.

COMMENT

Recurrence of the disease must be differentiated from recrudescence or relapse. Recrudescence may be defined as a reappearance of the symptoms or an extension of the paralysis within weeks of the original infection. Still [18] set a twelve week limit on these recrudescences and stated that there was no recorded case in which a second attack of the disease occurred after this three month interval for a period of two years from the original infection. He termed this a minimal duration of immunity, and his theory has been supported by many observers. Several investigators stated that this length of time appears to be excessive. The case we are presenting is characterized by a one year interval between attacks, and we believe this is the first such case to be reported.

It has been shown that the infection can be harbored by a child for four months and that the virus persists in the mouth and intestine of a child for as long as seven months. Lucas and Osgood [19] claimed that their patient carried the virus for two years and three months and was then reinfected with it.

It is possible that failure to acquire immunity from an attack of poliomyelitis is characteristic of only the unusual person or that an acute attack fails to produce adequate immunity in all persons. Other investigators suggested that of the many persons who are infected with the virus few have paralysis or clinically recognized poliomyelitis, and that the factor which determines the development of paralysis lies within the host. If this assumption is correct, a rate of 1 second attack per

16. Phelps, E. B.: Personal communication, cited by Fischer and Stillerman.[18]

17. Nelson, N. B., and Green, W. T.: Second Attack of Anterior Poliomyelitis: Report of Four Cases, Am. J. Dis. Child. **65**:757 (May) 1943.

18. Still, G. F.: Arch. Dis. Childhood **5**:295, 1930.

19. Lucas, W. P., and Osgood, R. R.: Transmission Experiments with the Virus of Poliomyelitis: Finding the Virus in the Nasal Secretion of a Human Carrier Four Months After the Acute Stage of a Second Attack of Poliomyelitis, J. A. M. A. **60**:1611 (May 24) 1913.

thousand cases would tend to show that in most persons an effective immunity was produced through the first attack. In other words, of those persons who are peculiarly susceptible to the disease, 999 out of every 1,000 acquire such resistance from the first attack that the second does not occur.

Development of the various strains of the poliomyelitis virus has led to the concept that second attacks of the disease are produced by a strain immunologically different from that causing the first infection. Toomey [8] warned that many times an acute infection may cause an exacerbation of or an increase in paralysis in patients who have had poliomyelitis.

Experimentally, it has been shown that monkeys can be reinfected several months to several years after they have recovered from the disease and that it is easier to reinfect monkeys with a different rather than with a similar strain of virus. Therefore, protection against second attacks seems to be relative, suggesting the importance of quantitative rather than qualitative variations in the strains of the virus.

SUMMARY

A case of recurrent poliomyelitis is presented and added to the few cases reported in the medical literature.

324 East Wisconsin Avenue (2).

News and Comment

SOCIETY NEWS

Meeting of International Society of Hematology Announced.—The International Society of Hematology will hold its biannual meeting at the Hotel Statler, in Buffalo, Aug. 23 to 26, 1948.

Time has been tentatively allotted for symposiums and presentations as follows: one-half day for general subjects, including radioactive and stable isotopes in hematology, one-half day for problems and diseases related to the red cells, one-half day for problems and diseases related to white cells, one day for immunohematology, Rh-Hr (CDE-cde) antigen and antibodies and hemolytic anemias, one-half day for problems in coagulation and hemorrhagic diseases and one-half day for the business meeting.

Scientific exhibits will be presented in the south wing of the seventeenth floor of Hotel Statler. Applications for the presentation of scientific exhibits are now being received by Dr. O. P. Jones, Department of Anatomy, University of Buffalo, Buffalo. The chairman of the program committee is Dr. Ernest Witebsky, Buffalo General Hospital, Buffalo.

Dr. Eduardo Uribe Guerola, Leibnitz 212, Nueva Colonia Anzurez, México, D. F., Mexico, is in charge of the program from South and Central America, and Sir Lionel Whitby, University of Cambridge, Cambridge, England, is in charge of arrangements for the program from Europe. Communications concerning applications for the program will be received by the aforementioned committeemen.

All scientific sessions and exhibits will be open to scientists interested in hematology, including, of course, members of the medical profession and workers in those branches of science dealing with hematology, such as biochemistry, biophysics, genetics and immunology.

Communications and applications concerning membership will be received by the following members of the membership committee:

Dr. William Dameshek, Chairman, 25 Bennett St., Boston, for the United States.

Dr. M. Bessis, Laboratoire de Recherches, Du Centre National de Transfusion Sanguine, 53 Boulevard Diderot, Paris, France.

Dr. Robert R. Race, Lister Institute, Chelsea Bridge Road, London, S. W. 1, England.

Dr. Ludwik Hirszfeld, Institute of Medical and Microbiologic Science, Wrocław, Poland.

Dr. Ignacio Gonzales Guzman, University of Mexico, College of Medicine, México, D. F., Mexico.

Dr. Walter Cruz, Instituto Oswaldo Cruz, Caixa Postal 926, Rio de Janerio, Brazil.

Dr. Alfredo Pavlovsky, Ancherena 1710, Buenos Aires, Argentina.

Dr. Theodore Waugh, McGill University, Montreal, Quebec.

Dr. Berger Broman, Royal Caroline Medical School, Stockholm, Sweden.

Dr. C. R. Das Gupta, Hematology Department, Calcutta School of Tropical Medicine, Calcutta, India.

Dr. Luis Sandoval S., Instituto de Histologia de la Universidad de Concepción, Santiago, Chile.

Dr. Rod Sirivejkul, Army Medical Department, Bangkok, Siam.

Dr. Carl Rohr, Medizinischen Universitätsklinik, Zurich, Switzerland.

Dr. Moises Chediak, Laboratories Chediak, 23 $654 Esq. A., Baños Vedado, Habana, Cuba.

Dr. G. di Guglielmo, Director of Medical Clinics, University of Naples, Policlinico, Naples, Italy.

Dr. Henrik Dam, Danmarks Tekniske Højskole, Biologisk Afdeling, Ostervolgade 10 Trappe L, Copenhagen, Denmark.

Those interested in attending the meetings may communicate with Dr. Sol Haberman, Secretary, The William Buchannan Blood Center, Baylor Hospital, Dallas, Texas.

GENERAL NEWS

Medical Journals Requested.—Requests from libraries, medical societies and individual physicians in various devastated countries are being received almost daily. If physicians have extra copies of medical journals or copies for which they have no further use, it will be greatly appreciated if they will send them to the headquarters of the American Medical Association for distribution abroad.

Special Volumes of Acta Pædiatrica Scheduled.—The following special volumes of *Acta Pædiatrica* will appear in the near future:

1. The Transactions of the Fifth International Pediatric Congress, New York, July 1947 (volume 36 of *Acta Pædiatrica*). Price, 25 Swedish crowns.

2. General index of volumes 1 to 30 of *Acta Pædiatrica*. Price, 15 Swedish crowns.

Orders should be sent to: *Acta Pædiatrica*, 30 Polhemsgatan, Stockholm, Sweden.

Examinations of the American Board of Pediatrics.—The American Board of Pediatrics will hold examinations on September 10, 11 and 12 in Seattle, and on November 17, 18 and 19 in Atlantic City, N. J.

Physicians Certified by the American Board of Pediatrics.—The following physicians were certified as specialists by the American Board of Pediatrics after examinations held at Chicago, June 26 and 27, 1948.

John H. Cordes Jr., St. Petersburg, Fla.; Victor J. Cordes, Wauwatosa, Wis.; Susan Coons Dees, Durham, N. C.; Harold X. Gerber, Chicago; John Roland Harvin, Sumter, S. C.; Maurice Kaufmann, Hempstead, N. Y.; John T. Kometani, New Orleans; William Caldwell Layton, Burlingame, Calif.; Jacob S. Light, Washington, D. C.; Bernard L. Lipman, Philadelphia; Dan Campbell McDougall, Pocatello, Idaho; Irving Howard Mauss, Belle Harbor, N. Y.; Evelyn E. Miller, Philadelphia; Dominic S. Motsay, Sayre, Pa.; Brian St. John Moynahan, Belleville, N. J.; Harry Thomas Nagel, Maywood, Ill.; Louis J. Needels, Santa Barbara, Calif.; Phyllis T. Mrazek Orland, Berwyn, Ill.; Herbert J. Palmer, New York; John Lyman Peck, Baltimore; Walter Pick, Fitchburg, Mass.; Bernard C. Prietsch, Pittsburgh; Francis Lupton Robinson, West Oakland, Calif.; Joseph L. Rubel, Pensacola, Fla.; Henrietta K. Sachs, Chicago; Joe M. Standefer, Des Moines, Iowa; Meritt W. Stark, Denver; Walter Milton Tasem, Los Angeles; Herbert Allan Wenner, Kansas City, Kan.; Norman C. Woody Jr., New Orleans, and Charles Richard Yoder, Bloomington, Ill.

Residency in Pediatrics at University of Arkansas Hospital.—Temporary approval has been extended by the Council of Medical Education and Hospitals of the American Medical Association to the residency in pediatrics offered at the University of Arkansas Hospital, Little Rock, Ark. This action has been taken in concurrence with the American Board of Pediatrics, which has indicated its acceptance of a two year training program.

PERSONAL NEWS

Appointment of Dr. Manuel Suárez.—Dr. Manuel Suárez Perdiguero has been made head of the department of Pediatrics and Child Health of the Facultad de Medicina of Santiago de Compostela, Spain.

Abstracts from Current Literature

Vitamins; Avitaminoses

A Comparison of the Vitamin C in Mothers and Their Newborn Infants. Lawrence B. Slobody, Reuel A. Benson and Joan Mestern, J. Pediat. **29**: 41 (July) 1946.

The comparative saturations of vitamin C in the tissue of mothers and their newborn infants were determined by means of the intracutaneous injection of a solution of sodium 2, 6-dichlorphenol indophenol. The infants were tested repeatedly during the first eight days of life. It was observed that the infants tended to show a saturation of vitamin C in the tissue irrespective of variations in the vitamin C concentration in the mother.

Grulee Jr., Minneapolis.

Prematurity and Congenital Deformities

Behavior Aspects of the Care of the Premature Infant. Arnold Gesell, J. Pediat. **29**:210 (Aug.) 1946.

The author describes the importance of tonal reactivity as the first evidence of behavior and as an index of the structural maturity of the organism. The possibility that optimal tonus may be provided by suitable close-fitting clothing, judiciously administered daily baths and brief skilful handling, as well as through bedding which imparts a sense of movement with the stirrings of the infant, should definitely have a place in the ideal management of the premature infant. No data referable to specific study are furnished.

Grulee Jr., Minneapolis.

Newborn

The Influence of Human Serum Albumin on Edema in Erythroblastosis Fetalis. Mendel Jacobi, Abraham Litvak and Seymour Gruber, J. Pediat. **29**:177 (Aug.) 1946.

Two infants with erythroblastosis fetalis complicated by severe generalized edema were given concentrated human serum albumin in addition to transfusions. In both patients elimination of edema was effected. The authors suggest that hepatic damage and disturbed blood protein levels are factors causing the production of the edema.

Grulee Jr., Minneapolis.

Treatment of Epidemic Diarrhea of the Newborn. Martin J. Glynn, J. Pediat. **29**:205 (Aug.) 1946.

Epidemic diarrhea of the newborn is discussed concisely, with a succinct, thorough, detailed review of therapy. The judicious use of starvation and subsequent gradual resumption of low caloric feedings, in combination with suitable replacement and subsequent maintenance therapy parenterally administered, are carefully related. The author reports mortality rates of 13 per cent among 91 full term infants under 4 weeks of age and of 17 per cent among 92 premature infants treated in this manner.

Grulee Jr., Minneapolis.

STATISTICAL PROBLEMS OF STILLBIRTH. FRANCISCO J. MENCHACA, Arch. argent. de pediat. **25**:147 (March) 1946.

Before the fight against stillbirths is organized on a rational, scientific basis, reliable statistics are needed. Fundamental methodologic reasons require that the nomenclature of the current "International List of Cases of Death" be followed, as well as the definitions of "stillbirths" and "perinatal mortality" given by the International Institute of Statistics. The accepted terminology must be widely disseminated, not only among physicians and obstetricians, but also among all those who deal with the statistics of stillbirth. The criteria for diagnosis that obstetrics will maintain in the next revision of the "Nomenclature of the causes of death" must be prepared sufficiently in advance.

It is necessary to secure accurate birth records and to perform autopsies on stillborn infants in order to establish the true causes of death. Social service is indispensable in establishing the cause of many stillbirths, and in reducing the mortality efficiently.

ROJAS, BOSTON.

Acute Contagious Diseases

TWO CASES OF WATERHOUSE-FRIDERICHSEN SYNDROME IN THE SAME FAMILY, ONE WITH RECOVERY UNDER PENICILLIN THERAPY. J. J. HOFFMAN and A. E. MAMELOK, Arch. Pediat. **63**:391, (Aug.) 1946.

Two cases of epidemic cerebrospinal meningitis (Waterhouse-Friderichsen syndrome) are presented. The patients were brothers, 13 and 15 years of age. The younger patient became ill first, with all the classic symptoms, and recovered after intensive therapy with plasma, dextrose and saline solutions, adrenal cortex extract, "percorten" (a proprietary preparation of desoxycorticosterone acetate), sulfadiazine and penicillin. Type II meningococci were cultured from the blood. Massive sloughing of the purpuric areas occurred, and residual pain in the joints lasted several weeks, but the prognosis was good.

The second patient was found dead in bed two days after his younger brother became ill. Autopsy revealed massive areas of purpura in the skin and massive hemorrhages in the adrenal glands. No culture of the blood was obtained.

The authors present a detailed review of the literature and a discussion of the optimal method of treatment. This treatment should include replacement therapy to compensate for involvement of the adrenal medulla and adrenal cortex, chemotherapy and general supportive measures. Emphasis is placed on rapid diagnosis and treatment.

DAVIS, Denver.

TREATMENT OF MENINGOCOCCIC MENINGITIS IN CHILDREN WITH A SINGLE INTRAVENOUS DOSE OF SODIUM SULFADIAZINE. SHERL J. WINTER, J. Pediat. **26**: 459 (May) 1945.

The 9 cases reported vary from the general method of treatment in that a single intravenously administered dose of sodium sulfadiazine of 2½ grains per pound of body weight (0.33 Gm. per kilogram) was given after alkalization with one-fifth molar sodium lactate (15 cc. per pound of body weight [33 cc. per kilogram]).

The patients ranged in age from 8 months to 7 years, and single doses ranged from 45 grains to 160 grains (3 to 10 Gm.). In most of the patients the temperature was normal in twenty-four hours, and in none did it continue to be elevated longer than seventy-two hours. The advantages of the single dose treatment may be enumerated as follows: First, only one venipuncture is necessary;

second, the blood and spinal fluids maintain an adequately high sulfadiazine concentration over a four day period for early recovery. (The blood level usually remains above 8 mg. for seventy-two hours and the spinal fluid level above 8 mg. for forty-eight hours.) Third, the clinical symptoms subside more rapidly than in the divided dose method of treatment; fourth, cultures of spinal fluid are sterile in twenty-four hours, thereby lessening the chance for sequelae and complications.

The following routine of treatment was employed in this series of cases:

1. Administration of sodium lactate (one-fifth molar), 15 cc. per pound of body weight (33 cc. per kilogram), is started by the method of intravenous drip.

2. Sodium sulfadiazine 2½ grains per pound of body weight is added to the remaining sodium lactate after half of the latter has gone into the veins. (The sulfadiazine is dissolved in 50 cc. of distilled water.)

3. Additional sodium lactate is given at a later period intravenously or subcutaneously, if indicated by the p_H of the urine or by the blood carbon dioxide.

4. Convulsions are controlled with paraldehyde (without benzyl alcohol), 1 cc. per 10 pounds of body weight (2.2 cc. per kilogram). This is given by gavage.

5. The p_H of the urine should be checked twice daily for four days, and a p_H of 7.5 or above should be maintained by giving additional sodium lactate if indicated.

Summary.—1. Nine patients were treated with a single intravenously administered dose of sodium sulfadiazine with no sequelae or complications.

2. If adequate alkalization is maintained, large doses of sodium sulfadiazine, intravenously administered, are well tolerated.

3. It is questionable whether the usual long period of quarantine is necessary with the present day treatment.

AUTHOR'S ABSTRACT.

IMMUNIZATION AGAINST WHOOPING COUGH. J. H. LAPIN, J. Pediat. **29**:90 (July) 1946.

The author reviews recently published experiences in a brief and concise discussion of immunization against whooping cough. He adds his observations of a series of 20 infants inoculated between 3 and 6 months of age, who were subjected to rapid agglutination tests for antibody titer three months after inoculation. Negative reactions were obtained in 60 per cent of this series of patients. The use of alum-precipitated preparations and of combinations of pertussis vaccine with diphtheria and/or tetanus toxoids is condemned as causing unnecessarily severe reactions, even formation of abscesses, in an appreciable number of infants. Pertussis vaccine alone in a concentration of 40,000,000,000 per cubic centimeter is recommended. Inoculation, in the opinion of the author, should begin when the infant is 6 to 9 months of age, with one injection per week until a total of 80,000,000,000 to 120,000,000,000 units have been given in three injections.

GRULEE JR., Minneapolis.

MUMPS: TECHNIQUES OF LABORATORY DIAGNOSIS, TESTS FOR SUSCEPTIBILITY, AND EXPERIMENTS ON SPECIFIC PROPHYLAXIS. JOHN F. ENDERS, J. Pediat. **29**:129 (Aug.) 1946.

A comprehensive discussion of the application of the complement fixation tests in the diagnosis of mumps and of the differential diagnosis of conditions simulating mumps meningoencephalitis is presented. Data are offered in support of the use of intradermal cutaneous testing with heat-inactivated virus as a measure of immunization against mumps. Clinical observation has indicated the ineffectiveness in prophylaxis of gamma globulin prepared from large pools of normal plasma. The results from the use of formalized vaccine for protection against the disease

are encouraging, if the vaccine is given prior to the incubation period of the disease. Finally, studies currently in progress on the production of active immunity through the use of mumps virus attenuated by egg passage are discussed.

GRULEE JR., Minneapolis.

MENINGOCOCCAEMIA: PART III. BACTERIOLOGY, SEROLOGY AND ETIOLOGY. W. R. LOGAN, Edinburgh M. J. **53**:235 (May) 1946.

The author discusses the mode of infection in meningococcic meningitis and its epidemiology. The primary infection is in the nasopharynx and is acquired from carriers, rather than from persons with active meningitis. Not all observers are agreed that there is an obvious local inflammation within the nasopharyngeal tract. The present view is that meningococcic meningitis may follow invasion of the blood stream by way of the lymphatic vessels from the nasopharynx. The primary site involved in the central nervous system is the lateral ventricles, through the choroid plexuses. It is probably a correct assumption that the portal of entry in meningococcemia is the same as that in meningitis, but it has not been so proved bacteriologically. The author discusses neurologic types of meningococci, as well as the types in meningococcemia; he makes a comparison of the pathogenicity and virulence of group I and group II as regards mortality and duration of the illness. The author discusses the intermittency in meningococcemia and the immunologic reactions in both meningococcemia and meningitis. He concludes that there is no evidence of the production of more protective substances in meningococcemia than in meningitis. Phagocytosis and lysis represent the first stage of a defensive process and are regarded as a protective action.

In most cases the disease was diagnosed by means of blood culture. The growth on culture usually is slow, requiring three or four days on the average. There is no positive information as to the optimal time for obtaining blood for culture in cases of meningococcemia; occasionally a positive culture may be obtained in a period of asphyxia. The author discusses the bacteriologic examination of cutaneous lesions. In acute and fulminating stages of infection, there are many meningococci in and beneath the skin. Toxins are released from the disintegrated micro-organisms which probably affect the endothelium of the capillaries, both in acute and in chronic meningococcemia.

NEFF, Kansas City, Mo.

PATHOGENESIS AND PREVENTION OF BRONCHOPNEUMONIA IN DIPHTHERIA. C. COMBA, Riv. di clin. pediat. **40**:1 (Jan.) 1942.

In the thirty-eight years after the introduction in 1894 of diphtheria antitoxin, 5,551 children with diphtheria were treated at the pediatric clinic in Florence, Italy. Of this number, 15.9 per cent died. Of the children without the complication of bronchopneumonia, 5.3 per cent died, while of the 1,021 with bronchopneumonia, 62.7 per cent died. Beginning in December 1932, a polyvalent antipneumococcus serum was used prophylactically in combination with the diphtheria antitoxin in the treatment of diphtheria. During the next eight years, the percentage of children with diphtheria in whom pneumonia developed dropped from 18.4 to 4.9 per cent, or to 2.6 per cent if one excluded those who already had bronchopneumonia on admission to the clinic. The incidence of diphtheria was highest in the group of children 4 to 7 years of age, but the mortality and the incidence of pneumonia was highest in the group from birth to 2 years of age.

HIGGINS, Boston.

Acute Infectious Diseases

DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY. V. STAPHYLOCOCCAL EMPYEMA: THE IMPORTANCE OF PYOPNEUMOTHORAX AS A COMPLICATION. GILBERT B. FORBES, J. Pediat. **29**:45 (July) 1946.

A careful and complete discussion of the cases of staphylococcic empyema observed at the St. Louis Children's Hospital during the past ten years is presented, not including those in which penicillin was used. One half of all cases of empyema in infants under 1 year of age were caused by the staphylococci, as compared with 10 per cent in the entire pediatric age group. The pathologic changes caused by staphylococcic pneumonia are discussed in relation to the frequent occurrence of bronchopleural fistulas and consequent pyopneumothorax. The latter complication is considered by the author as being most dangerous and demanding immediate closed intercostal syphon drainage. Pyopneumothorax occurred in 2 of every 5 cases in the series. The total mortality rate of 26.2 per cent is discussed in relation to the progressively improved management of the patients. Early diagnosis and vigorous therapy, including chemotherapy with sulfonamide compounds, are emphasized, as well as the application of all suitable supportive measures and the prompt surgical drainage of the pyopneumothorax. It is concluded that antistaphylococcic serum is of limited usefulness and that sulfonamide drugs, though not highly effective, should be used.

GRULEE JR., Minneapolis.

DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REVIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY. VI: ACUTE ILIAC LYMPHADENITIS. MERL J. CARSON and ALEXIS F. HARTMANN, J. Pediat. **29**:183 (Aug.) 1946.

The clinical syndrome presented by 11 patients with iliac lymphadenitis is discussed, together with the differential diagnosis and treatment of the condition. In the authors' opinion, pain in the abdomen, hip, thigh or knee, psoas spasm with protective flexion of the thigh on the abdomen and free motion of the hip joint, except for extension of the thigh, are particularly suggestive signs. Fever and leukocytosis are the commonest observations and hemolytic Staphylococcus aureus the most frequent causative organism. Subcutaneous administration of penicillin, in addition to sulfonamide therapy, is recommended in treatment.

GRULEE JR., Minneapolis.

SALMONELLA ANATUM INFECTION. PHILIP J. ALMADEN and JOEL WAHLIN, J. Pediat. **29**:199 (Aug.) 1946.

This report includes 8 cases of infection with Salmonella anatis that were seen over thirteen months. Three of the 8 cases occurred in March 1944. In these 3 cases the discovery of the salmonella organism was incidental. It was recovered from the pleural fluid in a child with empyema due to pneumococci. The second child had bilateral pneumonia, with abdominal distention. The third child had osteomyelitis, with septicemia and bronchopneumonia. The organism was recovered from the feces of these 2 children.

In February and March 1945 an institutional outbreak of 5 cases of enteritis due to S. anatis occurred in an isolation ward after the introduction of an initial case from the obstetric nursery. The clinical picture was a moderate enteritis of the type classified by Hormaeche as dysenteriform. This type is characterized

by an abrupt onset, liquid green stools containing blood and mucus, a moderate febrile reaction and relatively short duration. Prompt attention to the condition may have been responsible for the mild nature of the outbreak.

The initial case was in a newborn infant with the primary complaint of enteritis. The second infant was admitted for treatment of severe tracheobronchitis; a third had conjunctivitis and an infection of the upper respiratory tract; a fourth was admitted with bronchopneumonia, and the fifth infant had a fracture and signs of mild infection of the upper respiratory tract.

Although the number of cases is too limited to warrant definite conclusions, the question naturally arises of the role played by infection of the respiratory tract in lowering resistance and thereby paving the way for salmonella infection.

Bornstein noted that sulfaguanidine was not effective in controlling all salmonella infections. Many pediatricians use sulfadiazine as chemotherapy for enteritis. In the present series it was observed that sulfadiazine given for treatment of the infection of the respiratory tract did not prevent the development of the enteritis.

S. anatis was isolated from ducklings by Rettger and Scoville and from flies by Hormaeche and his co-workers. The mild weather at the time these cases occurred permitted the ingress of flies. The fact that a flock of ducklings were kept for experimental purposes in the vicinity of the hospital at that time suggests that transmission by insects may have occurred. Examinations of stools of all hospital personnel involved revealed no pathogens. Inasmuch as only one specimen from each attendant was cultured, the possibility of a carrier among the food handlers was not excluded entirely. Since the infection was limited to one ward, it is possible that the mode of transmission was from patient to patient by the hands of attendants and that only those patients with low resistance contracted the enteritis.

FROM THE AUTHORS' SUMMARY.

LEISHMANIASIS IN SARDINIA. G. MARIA DORE, Pediatria **55**:109 (Jan.-March) 1947.

The author describes 5 cases of visceral leishmaniasis observed since 1940 among children living in Sassari province.

FROM THE AUTHOR'S ABSTRACT.

TESTS OF INFECTIVITY WITH OXYURIS. N. H. SWELLENGREBEL, Nederl. tijdschr. v. geneesk. **90**:762 (July 6) 1946.

As it was unknown whether desiccated eggs of Oxyuris, especially those present in dust, could still develop into full grown worms, the author made this investigation. The dust was taken from an open air school where almost 100 per cent of the children were infected with Oxyuris. The dust, at least three days old, was washed in 0.2 per cent hydrochloric acid and centrifuged; then the number of eggs was counted. The dust was then dropped on bread and eaten. The number of eggs swallowed by each volunteer varied between 40 and 80.

Six of the eight tests with the egg-laden dust produced the infection. To determine exactly the first manifestation, a perianal preparation was made each day; the shortest incubation period appeared to be thirty-seven days. The excretion of the worms, as shown by the presence of eggs, lasted twelve to twenty-seven days. It appeared that such an infection with Oxyuris disappeared spontaneously if contamination with fingers or dust could be prevented. Eggs from dust always produce slight infection, whereas eggs from fingers may give rise to severe infections.

As regards the treatment of oxyuriasis, one must always bear in mind that infection from dust is a factor which is not under control. For this reason, the author rejects severe purging of patients with oxyuriasis, as well as the administration of high enemas. He is of opinion that only so-called active oxyuriasis, i. e., infection giving rise to complaints, should be treated.

The treatment should not be complicated, and only nonirritating methods should be used until the outlook for radical means of combating the infection has become better. New insight into the significance of egg-laden dust in schools makes the author skeptical as to the possibility of stamping out an Oxyuris infection in a whole family.

VAN CREVELD, Amsterdam, Netherlands.

TEN YEARS OF SPRAYING HOUSES AGAINST MALARIA. N. H. SWELLENGREBEL and H. KRAAN, Nederl. tijdschr. v. geneesk. **90**:1377 (Oct. 12) 1946.

The authors report on ten years' observation on the effect of house spraying with pyrethrum solutions during the period of transmission of malaria (August to October). Malaria was greatly reduced in rural areas, and these areas withstood even the severe epidemic which started in 1944. In urban areas the results were unsatisfactory.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

PERSISTENT RIGHT AORTIC ARCH WITH ATRESIA OF THE ENTIRE MAIN PULMONARY ARTERY. PETER A. HERBUT and ROBERT J. FOX, Am. Heart J. **31**:490 (April) 1946.

Of the many anomalies that may arise from the primitive aortic arches present in the developing human embryo, atresia of the main pulmonary artery is one of the least frequently encountered. A combination of this abnormality with a right-sided aortic arch is even less frequent, for the literature contains only one report of such a case. The case presented is that of an infant who became cyanotic two days after birth and died on the fourteenth day of extrauterine life. Necropsy revealed atresia of the entire main pulmonary artery, a right-sided aortic arch, patent right ductus arteriosus, interauricular and interventricular septal defects and dextroposition of the aorta.

FROM THE AUTHORS' SUMMARY.

DIFFERENTIATION OF TYPES OF TUBERCLE BACILLI WITH THE MEDIUMS OF PETRAGNANI. G. C. ABBA, Riv. di clin. pediat. **40**:40 (Jan.) 1942.

Petragnani describes a medium containing 5 per cent glycerin U. S. P. on which the human type of tubercle bacilli grows abundantly and a medium containing 1 per cent "virgin wax" on which the bovine type thrives. Abba used these mediums to differentiate between the two types in the tubercle bacilli he found in 20 patients with tuberculous meningitis. He reported that in 12 cases the bacilli were of the human type, in 6 of the bovine type and in 2 identification was doubtful. The test should be of value in establishing the source of the infection.

HIGGINS, Boston.

Diseases of Blood, Heart and Blood Vessels and Spleen

ELECTROPHORETIC ISOLATION OF A CIRCULATING ANTICOAGULANT. F. L. MUNRO and MURIEL PLATT MUNRO, J. Clin. Investigation **25**:814 (Nov.) 1946.

Plasma from a patient with hemophilia was electrophoretically fractionated in a Tiselius cell. Two fractions were removed from each side of the cell under observation with the Toepler Schieren method. The fractions were tested for

anticoagulant activity by determination of the extent to which they would prolong the coagulation time of recalcified normal plasma.

Only the fractions containing gamma globulin displayed anticoagulant activity. Both the gamma globulin plus fibrinogen fraction and the gamma and beta globulin plus fibrinogen fraction showed anticoagulant activity. On removal of fibrinogen, and with further electrophoretic fractionation, it was shown that the anticoagulant activity was within the gamma globulin fraction.

BRODSKY, Cincinnati.

LABORATORY AND CLINICAL CRITERIA OF RHEUMATIC CARDITIS IN CHILDREN. L. M. TARAN, J. Pediat. **29**:77 (July) 1946.

The author presents a series of 200 patients from 6 to 14 years of age who had rheumatic fever without signs of cardiac failure. They were studied under well controlled conditions for at least six months after the onset of carditis. In a search for suitable laboratory criteria for determining the presence of carditis, the following measurements were made and were found inadequate: leukocyte counts, temperature, auriculoventricular conduction time, pulse rate, sedimentation rate, gain in weight, hemoglobin values and vital capacity. The results of the last mentioned test were considered the most helpful. Similarly, the following clinical criteria were appraised: fatigability, emotionality, degree of pallor, lability of pulse rate, changes in cardiac rhythm, evidence of progressive cardiac damage and the evanescent quality of heart sounds and murmurs. In many instances these factors were helpful, but in no case could they be considered pathognomonic. The author concludes that clinical judgment based on long and careful observation of patients with rheumatic fever is the best criterion. The importance of rest in bed as treatment is emphasized.

GRULEE JR., Minneapolis.

CONGENITAL AORTIC ATRESIA. NORMAN H. ISAACSON, SAMUEL D. SPATT and DAVID M. GRAYZEL, J. Pediat. **29**:222 (Aug.) 1946.

One of the rarest of congenital cardiac anomalies, complete fusion of the aortic cusps, with resulting hypoplasia of the left side of the heart and the ascending aorta, is described in this report. In the 7 cases previously reported, the average length of life was four days. Cardiac murmurs were heard in only 2 of the 7 cases.

Baby K. was cyanotic and dyspneic at birth. No murmurs were heard on auscultation of the heart. Physical examination revealed nothing remarkable. The baby died approximately forty-eight hours after birth.

At postmortem examination the heart weighed 18 Gm. The ascending aorta was narrowed, and the pulmonary artery was dilated. Both vessels originated from their normal locations. The aortic orifice was entirely closed by fusion of the valvular cusps. The ductus arteriosus was widely patent. The left atrium and ventricle were atretic, and the right atrium and ventricle were dilated. The kidneys were grossly congested and hemorrhagic, and the lungs were atelectatic. The remainder of the organs showed severe congestion.

In this case it may be assumed that there was an infection of the aortic valve, with resulting atresia, when the heart was still quite small. After this lesion, the proportionate growth of the left ventricle and the ascending aorta ceased, and the right ventricle, which carried the entire circulatory load, became correspondingly dilated and hypertrophied. Similarly, the ductus arteriosus became extremely large because it performed the function of the ascending aorta, as well as its own.

FROM THE AUTHORS' SUMMARY.

NONLIPID RETICULOENDOTHELIOSIS (ACUTE CRYPTOGENIC ALEUKEMIC RETICULOENDOTHELIOSIS). GUSTAVO PITTALUGA, AGUSTÍN CASTELLANOS, ENRIQUE GALÁN JUAN JIMÉNEZ and LUIS BARRERAS, Rev. cubana de pediat. **18**:125 (March) 1946.

In a case of nonlipid reticuloendotheliosis in a boy 9 years of age the clinical picture was characterized by gradual onset of pallor and by asthenia, anorexia, general malaise and protracted fever. The initial symptoms were referable to the respiratory tract, with clinical and roentgenologic evidence of pulmonary consolidation. There were splenomegaly, moderate hepatomegaly and polyadenopathy. The disease lasted four months. The child died in collapse, as a result of uncontrollable hemorrhage from the lungs.

Hematologically, there were progressive anemia, leukopenia, neutropenia and thrombopenia. There finally appeared in the blood large numbers of atypical cells with the morphologic character of histiocytes. Examination of specimens obtained by puncture from the sternal bone marrow, the lung, the spleen, the liver and the lymph nodes permitted the diagnosis of nonlipid reticuloendotheliosis to be made during the child's life.

The cause of the process was not determined. There was a generalized hyperplasia of the cells of the reticuloendothelial system, both monocytes and histiocytes No lipid foam cells were observed at any time. The authors expressed the opinion that the patient had a condition differing from that known as Letterer-Siwe disease. There were lesions in the bones, and the blood picture varied from that reported in the aforementioned disease.

There is a detailed discussion of the literature and of the distinct clinical and anatomic entities referred to as "reticuloendotheliosis." KEITH, Rochester, Minn.

HISTORICAL, CLINICAL, HEMATOLOGIC AND BIOCHEMICAL REPORTS AND PATHOGENIC CONSIDERATION OF TWENTY-FIVE CASES OF MEGALOBLASTIC HYPERCHROMIC ANEMIA IN EARLY INFANCY. MAURO AMATO, Pediatria **54**:71, 1946.

During the last four years the author had the opportunity to observe in the pediatric clinic of Naples 25 cases of megaloblastic hyperchromic anemia in infants. Because of the rarity of this syndrome during the first months of life, and because there are few references to it in the literature, the author calls attention to the principal anamnestic, clinical, hematologic and biochemical data obtained in these cases.

The anemia in these cases responded rapidly to the administration of liver extract with a high content of the anti-pernicious-anemia principle, whereas the oral administration of large doses of beer ferment, in some instances for fifteen to thirty days before the initiation of liver therapy, gave no results.

In none of the children was recurrence observed; so it seems that this form of anemia is susceptible to definite, or at least prolonged, remission.

The author discusses the etiologic and pathogenic aspects and concludes that, in the cases he observed, one can speak of Biermer's (pernicious) anemia only when it is shown that the form of anemia is cryptogenetic and is due to a deficiency of Castle's intrinsic factor.

The disturbance of the production of the intrinsic principles seems usually to be functional; the author, therefore, advances the hypothesis that children with this type of anemia at birth have a functional incapacity to produce this ferment and that administration of a preparation containing the anti-pernicious-anemia principle will stimulate and carry into action the production of this ferment.

FROM THE AUTHOR'S ABSTRACT.

ELECTROCARDIOGRAPHIC STUDY OF 156 ELEMENTARY SCHOOL CHILDREN. G. MATTOLI and A. SEGANTI, Riv. di clin. pediat. **40**:273 (May) 1942.

Electrocardiograms were made for 156 school children with actual or potential pathologic lesions of the heart, as reported by the school physicians. The observations in this project led to the recommendation that electrocardiograms be made for all school children suspected of having cardiac disease in order to prevent and limit damage to the heart.

HIGGINS, Boston.

Diseases of Nose, Throat and Ear

CRANIOPHARYNGIOMAS IN CHILDREN. F. D. INGRAHAM and H. W. SCOTT JR., J. Pediat. **29**:95 (July) 1946.

The authors present their experience with 16 cases of craniopharyngioma, of which 12 were from 1 clinic and constituted 6.3 per cent of the intracranial tumors studied in that clinic over thirteen years. Two reports of illustrative cases are included. The histologic differentiation of the tumors as mucoid epithelial cysts, adamantinomas or squamous epitheliomas is described. The authors discuss the cardinal symptoms of visual disturbances, intracranial hypertension, hypophysial disorders and hypothalamic disorders. Aids to diagnosis, such as discovery on roentgenographic examination of the skull of suprasellar calcification and evidence of increased intracranial pressure, are pointed out. Although, frequently, complicated neurosurgical approaches are necessary in individual cases, frontal craniotomy, with resection of a portion of the cyst, is recommended whenever possible. The authors express the opinion that postsurgical irradiation should have further trial.

GRULEE JR., Minneapolis.

Diseases of Lungs, Pleura and Mediastinum

CONGENITAL CYSTIC DISEASE OF THE LUNG. JOE GARDNER, New Orleans M. & S. J. **99**:15 (July) 1946.

Congenital cystic disease of the lung is not a rare condition. Because of the variety of its manifestations it has been described in medical literature under eighteen names, which are enumerated in the article. The author gives two popular classifications—Koontz's and Sellers'.

The disease was first described by Fontanus in 1638. Interest was renewed after the report by Koontz, in 1925. At present reports of the disease are fairly common. In many cases the condition is asymptomatic, being accidentally discovered at autopsy. Bronchiectasis is the commonest condition to be confused with cystic disease. One or both lungs may be involved. Incidence is similar for the two sexes. No routine treatment can be given, owing to the wide variation in types.

BERKLEY, Beverly Hills, Calif.

PENICILLIN INHALATION IN PULMONARY DISEASE. J. H. HUMPHREY and H. JOWLES, Lancet **2**:221 (Aug. 17) 1946.

The authors tested a small number of patients for the presence of penicillin in the sputum after intramuscular injection. In patients with lobar pneumonia it was possible to detect the drug regularly, whereas in those with bronchiectasis, purulent bronchitis and pulmonary abscess this was rarely possible. After 15,000 to 30,000 units of penicillin had been inhaled in a spray, the drug was present in the sputum in a concentration of 1 or more units per cubic centimeter for four hours. It was also present in the blood and could be recovered in the urine.

Eighty patients with chronic pulmonary disease were given an average daily dose of 90,000 units at four hour intervals, with one rest period during the night. Bacteriologically, there was a virtual disappearance of gram-positive cocci by the fourth day of treatment. Gram-negative rods, including Proteus vulgaris, Pseudomonas aeruginosa and penicillin-resistant strains of Hemophilus influenzae and Hemophilus parainfluenzae, increased.

Clinical improvement was greatest in patients with chronic bronchitis and those with cardiac failure with superimposed disease of the respiratory tract. The results with chronic bronchiectasis were felt to be good. The patients were graded on subjective improvement, output of sputum, pyrexia, dyspnea, roentgenologic picture and white blood cell counts.

RICHARD G. HODGES, Cleveland.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

THE CONTROL OF DIARRHEA BY TOMATO POMACE. LESTER M. MORRISON, Am. J. Digest. Dis. **13**:196 (June) 1946.

Pulverized, dehydrated tomato pulp (tomato pomace) was used to treat more than 100 patients with various types of diarrhea. One tablespoon (15 cc.) ot pomace was given every three hours to the patient with moderate diarrhea, and 1 tablespoon after every bowel movement to the patient with severe diarrhea. Relief of symptoms and normal stools were observed after twenty-four hours in the usual case and after forty-eight hours in the severe case. Nine cases are reported in detail. No control series is mentioned.

KIMBALL, Evanston, Ill.

FOREIGN BODY IN DUODENUM CAUSING URINARY DISTURBANCE. E. T. McENERY and P. F. Fox, J. Pediat. **29**:226 (Aug.) 1946.

A case is reported of persistent hematuria, albuminuria and pyuria which were attributable to inflammatory adhesions in the region of the third portion of the duodenum and involving the right kidney, resulting from the presence of a bobby pin within the duodenal lumen. Uneventful recovery followed surgical removal of the foreign body.

GRULEE JR., Minneapolis.

HIRSCHSPRUNG'S DISEASE. WILFRID SHELDON, Practitioner **156**:425 (June) 1946.

Congenital dilatation of the colon (Hirschsprung's disease) is characterized by progressive distention, elongation and hypertrophy of the large intestine and occurs more frequently in male patients. Symptoms appear within the first few weeks of life; the course is unknown. The abnormality extends from the cecum to the rectum, with the most pronounced distention in the pelvic portion of the colon. Occasionally, the lower end of the small intestine is involved, but the anal canal is not affected. There is no demonstrable obstruction by valves or bands. True Hirschsprung's disease is to be distinguished from dilatation of the colon arising from a demonstrable obstruction, such as a rectal stricture. The two most striking symptoms are conspicuous enlargement of the abdomen and severe constipation. Of 30 patients with Hirschsprung's disease, 14 died in the first year and 2 in the first month. A few children with the disorder reach adult life.

Medical treatment consists chiefly in the administration of drugs which stimulate the action of the parasympathetic nervous system, such as methacholine chloride U. S. P. (acetyl-β-methylcholine chloride), pilocarpine, physostigmine and neostigmine. Atropine derivatives have been used, with reportedly good results.

Surgical treatment recently has consisted of bilateral division of the second to the fourth lumbar sympathetic rami. Good results have followed this operation in that the child has a daily bowel action without the use of laxatives.

Spinal anesthesia, which to be effective should be complete to the fifth thoracic root, has produced permanent benefit, but usually constipation gradually returns. This procedure serves as a guide in the selection of patients most apt to benefit permanently from sympathectomy. No known treatment reduces appreciably the size of the abdomen.

DIARRHEAS OF VIRUS ORIGIN IN SUCKLINGS. JACQUES GERBEAUX, Arch. franç. d. pediat. **3**:420, 1946.

The notable contributions of American clinicians in the clarification of severe diarrheas of infants and children are reviewed. Particular credit is given to the investigations of Barenberg, Baker, Light and Hodes, Katherine Dodd and John Budding. The isolation of a virus hitherto unrecognized in cases of stomatitis and diarrhea is discussed, and the clinical features of the disease, together with the results of inoculation, are adequately presented.

AMESSE, Denver.

PYLOROSPASM AND PYLORIC HYPERTROPHIC STENOSIS IN INFANTS. A. INGIULLA, Riv. di clin. pediat. **40**:13 (Jan.) 1942.

Three infants with severe pyloric stenosis and 2 with pylorospasm stopped vomiting and began to gain weight almost immediately after the institution of epinephrine therapy, 2 to 5 drops before each feeding.

HIGGINS, Boston.

BACTERICIDAL PROPERTIES OF THE SALIVARY GLANDS. MARY CRISALLI and L. SANNA, Riv. di clin. pediat. **40**:47 (Jan.) 1942.

Measured cultures of Escherichia coli, Eberthella typhosa, Salmonella paratyphi and staphylococcic organisms were added to mediums containing sterile macerated pulp from the submaxillary glands of oxen. The number of living organisms in each culture gradually diminished, resulting in complete sterilization in four hours. It is suggested that this bactericidal property explains the rare occurrence of bacterial infection of the salivary glands.

HIGGINS, Boston.

ESOPHAGEAL DYSTONIA AND DYSKINESIA IN CHILDREN. G. GUASSARDO, Riv. di clin. pediat. **40**:285 (May) 1942.

Two cases of functional obstruction of the esophagus in children are reported. One child had dystonia and the other dyskinesia. Differentiation was made by the administration of a preparation of belladonna, which relieved the esophageal spasm of the child with dystonia. The ratio of potassium to calcium in the blood was higher in this child.

HIGGINS, Boston.

HEPATITIS WITH SYMPTOMS OF CIRRHOSIS OF THE LIVER IN A BABY. A. VAN WESTRIENEN, Nederl. tijdschr. v. geneesk. **90**:684 (June 22) 1946.

During an epidemic of hepatitis a baby 6 months had slight symptoms of hepatitis without jaundice, followed by alarming symptoms of cirrhosis of the liver. Later, all these symptoms disappeared and the baby completely recovered.

VAN CREVELD, Amsterdam, Netherlands.

FAMILIAL CIRRHOSIS OF THE LIVER AND OSTEOPOROSIS. A. G. SCHOO, Nederl. tijdschr. v. geneesk. **90**:700 (June 22) 1946.

A case of hepatic osteoporosis with familial cirrhosis of the liver is described. Treatment with a massive dose of vitamin D gave temporary relief from the pain in the legs.

VAN CREVELD, Amsterdam, Netherlands.

REVERSIBLE FORM OF MEGACOLON. F. L. J. JORDAN, Nederl. tijdschr. v. geneesk. **90**:1292 (Oct. 5) 1946.

In this clinical lecture, the author describes 2 patients with short attacks of fever occurring during the war days. In both cases roentgenographic studies revealed great dilatation of the colon and dolichocolon. With a diet low in cellulose, the attacks of fever and other complaints soon disappeared. The author concludes that in addition to the congenital dilatation of the colon (Hirschsprung's disease) there was present a temporary noncongenital dilatation of the colon. The latter condition is probably the result of an atony, which arises in predisposed patients under the influence of a wartime diet abnormally rich in cellulose. During the attacks of fever, 1 of the 2 patients also had rheumatic complaints and red spots on the skin.

VAN CREVELD, Amsterdam, Netherlands.

EXPERIMENTAL EPIDEMIC HEPATITIS. J. D. VERLINDE, Nederl. tijdschr. v. geneesk. **90**:1309 (Oct. 5) 1946.

The virus of epidemic hepatitis was observed by means of inoculation of guinea pigs with the blood, urine and feces of patients with the disease. The virus causes specific changes (hyaline necrosis) in the liver of the guinea pig, which could be observed histologically in animals killed ten to twenty days after onset of infection.

VAN CREVELD, Amsterdam, Netherlands.

Nervous Diseases

STREPTOMYCIN IN THE TREATMENT OF INFLUENZAL MENINGITIS. JOHN R. BIRMINGHAM, ROBERT KAYE and MARGARET H. D. SMITH, J. Pediat. **29**:1 (July) 1946.

Reports are presented of cases of influenzal meningitis in 8 children treated exclusively with streptomycin, both intramuscularly and intrathecally, or with the antibiotic substance in combination with a sulfonamide drug and anti-Hemophilus influenzae type B serum (rabbit). Four patients recovered. Three patients died, and streptomycin therapy for 1 patient was abandoned because of apparent lack of response. In the last-mentioned patient development of fastness to the drug was demonstrated. Toxic reactions at the injection site, principally local pain, cutaneous eruptions and augmentation of meningeal signs, occurred but were not serious. The authors conclude that streptomycin is effective against Hemophilus influenzae type B and that its further clinical trial in influenzal meningitis is warranted.

GRULEE JR., Minneapolis.

INFLUENZAL MENINGITIS: REPORT OF THREE CASES TREATED WITH STREPTOMYCIN AND SULFADIAZINE. SYDNEY NUSSBAUM, SOLOMON GOODMAN, CLARENCE ROBINSON and LOUIS RAY, J. Pediat. **29**:14 (July) 1946.

Three infants, 9, 16 and 15 months of age, respectively, with influenzal meningitis were treated with streptomycin both intrathecally and intramuscularly, as

well as with sulfadiazine. Streptomycin, 50,000 micrograms, was given intrathecally daily until clinical response was evident; to maintain an antibacterial level in the blood stream, 50,000 micrograms was given intramuscularly every three hours until 3 Gm. had been injected. In the opinion of the authors, the rapid, dramatic improvement in these infants was undoubtedly attributable to the antibiotic substances.

GRULEE JR., Minneapolis.

TRIDIONE, ITS USE IN CONVULSIVE AND RELATED DISORDERS. M. A. PERLSTEIN and M. B. ANDELMAN, J. Pediat. **29**:20 (July) 1946.

The authors present their experience in the use of trimethadione ("tridione" or 3,5,5-trimethyloxazolidine-2,4-dione) in a group of 75 persons, two thirds of whom were between the ages of 5 and 15 years. The disease condition in 50 per cent of the subjects was diagnosed as epilepsy, the number of persons with organic brain disease and the number of those with idiopathic brain diseases being equal. The remainder of the patients had cerebral palsy, dystonia musculorum, behavior disturbances, tetanus, chorea and paralysis agitans. The dose given orally varied from 2.5 grains (0.16 Gm.) twice daily to 10 grains (0.65 Gm.) five times a day (intravenous and intramuscular administration was used in patients with tetanus).

Disappointing results were obtained with the use of the drug for persons with organic epilepsy. Greatest improvement, however, was noted in some patients subject to petit mal attacks. In contrast, trimethadione greatly benefited the majority of those with idiopathic epilepsies, again particularly the group with the petit mal form. In grand mal attacks its value was greatest when used in combination with phenobarbital, but it was not considered an effective primary anticonvulsant. At least a temporarily beneficial effect was noted in the management of behavior disturbances. The authors express the belief that trimethadione exerted a beneficial effect on persons with athetosis but was of little value in those with the spastic and dystonic types of cerebral palsy. Patients with chorea were not benefited. Good results were apparently obtained in the treatment of tetanus in 1 of 2 children in a series of 5 patients. Few side effects were noted, and toxic symptoms, such as visual disturbance or dizziness, occurred in less than 10 per cent of the patients. The authors suggest the site of action of trimethadione may be in the midbrain, the basal nuclei or the cortical connecting tracts of these centers.

GRULEE JR., Minneapolis.

HEMORRHAGIC ENCEPHALITIS WITH MENTAL SEQUELAE. F. LÓPEZ CLARES, MARÍN RAMOS C. and MARGARITO CASTAÑEDA, Bol. méd. d. Hosp. inf., México **2**:375 (Jan.-Feb.) 1946.

R. R. A., a 5 year old boy, was admitted to the hospital because of convulsions, unconsciousness and vomiting. At the physical examination the patient was found to have a number of neurologic signs and symptoms which, together with the data obtained from the laboratory, established the diagnosis. The patient was treated with sulfadiazine, 37 Gm. in all; 2,180,000 units of penicillin, and paraldehyde. Four months later, the child was discharged, but his mentality had not returned to normal. The psychiatrist in charge believed that the prognosis was not good since the last mental test showed no improvement over the previous one done two and a half months previously.

MADERO, México, D. F., Mexico.

PONTINE TUMORS IN INFANCY. T. A. E. JANSSEN, Ann. pædiat. **166**:1 (Jan.) 1946.

The author found in the literature 5 cases of tuberculoma pontis in infants less than 1 year old. She herself observed an infant whose symptoms first appeared at the age of 3½ months. The child died when 9 months old. At necropsy a ganglioglioneuroma of the pons was found which had invaded the medulla oblongata and the left cerebellar hemisphere. The author's patient exhibited symptoms more varied than the symptoms reported in the literature, probably because the tumor was more extensive and had invaded more tissue. AUTHOR'S SUMMARY.

Psychology and Psychiatry

CHILD PSYCHIATRY AND THE PRACTICE OF MEDICINE. HAROLD A. GREENBERG, Illinois M. J. **90**:279 (Nov.) 1946.

Greenberg points out that child psychiatry can contribute more to the understanding of the psychologic aspects of medicine than can any other section of psychiatry. The development of a person's character or personality can be seen clearly as one works with children.

The Illinois Institute for Juvenile Research has been concerned with the genesis, diagnosis and treatment of emotional and behavior problems of children, and in the wider implications of these problems. It hopes to further the understanding and prevention of those psychologic difficulties in children which result in somatic disturbances in the adult. It has also been interested in teaching the use of those psychotherapeutic technics which can be used by the average physician. Three case histories are given as illustrations.

The average physician has a basic requirement for successful psychotherapy, namely, the confidence of the patient, and from this point he can easily develop other technics. Often the physician's support in the form of encouragement, appreciation of the patient's attempts to help himself and the simple acceptance of the patient's complaints may be enough.

O. BARBOUR, Peoria, Ill.

PSYCHIATRY IN THE ILLINOIS STATE TRAINING SCHOOL FOR BOYS. JOHANN R. MARX, Illinois M. J. **90**:290 (Nov.) 1946.

Marx believes that sufficient clinical diagnostic facilities should be provided for study of the individual boy. Material obtained in these studies should be utilized for statistical analysis and research in therapy.

There is a definite need for active psychiatric and group treatment of a large majority of the boys, who are treatable. Resistive boys should be subjected to experimentation with new technics. If their influence seriously disrupts the training program, administrative elimination is recommended. Since every employee working with boys exercises a strong favorable or unfavorable influence, careful selection of new employees and individual attention to their emotional needs should be given.

Much closer contact should be maintained between the training school and various organizations interested in the treatment of delinquency. Special efforts should be made to assure acceptance by the community of individual boys and the training school program as a whole. Continuous public education emphasizing that delinquency is a symptom of a socially ill person and assistance by the public in providing adequate means of satisfying the needs of such a person are recommended.

O. BARBOUR, Peoria, Ill.

Diseases of the Genitourinary Tract

BILATERAL RENAL AGENESIS. EDITH L. POTTER, J. Pediat. **29**:68 (July) 1946.

Twenty cases of complete renal agenesis discovered in the course of 5,000 autopsies on fetuses and newborn infants are reported, together with a review of the literature. Seventeen of the cases were in male infants, and in all patients hypoplasia of the lungs, as well as a characteristic facies, was observed. A comprehensive discussion of probable embryonic aberrations is included.

GRULEE JR., Minneapolis.

MALIGNANCY OF THE GENITOURINARY TRACT IN CHILDREN: REPORT OF A CASE OF SARCOMA OF THE VULVA. ALLEN C. SERVICE and R. C. DERBYSHIRE. J. Pediat. **29**:228 (Aug.) 1946.

A case of fibromyxosarcoma of the vulva in a 3 year old child is presented, and the literature on malignant tumors of the genitourinary tract in children is reviewed. Malignant growths in this region in children are extremely rare. Only 1 case similar to the 1 under consideration was found, that reported by Taussig in 1931.

The patient, a 3 year old white girl, was first examined in May 1945, when she had a large mass protruding from the vagina. When the child was 13 months of age, the mother had noticed a small nodule just inside the vagina; this steadily increased in size until it interfered with locomotion.

The family history and the past history were irrelevant, except for the occurrence of carcinoma of the stomach in the maternal grandfather.

Examination revealed a fungating, infected mass which protruded from the vagina and measured 13 by 10 by 7.5 cm. Its exact site of attachment and the location of the external urethral orifice could not be determined at the initial examination. There was no enlargement of the regional lymph nodes, and a roentgenogram of the chest showed no evidence of metastasis. On the general physical examination considerable emaciation was evident; tachycardia was present, as well as a systolic murmur most pronounced at the apex of the heart.

On June 4, after a week of preparation in the hospital, surgical removal of the tumor was undertaken. With the patient under ether anesthesia a more detailed examination could be made. The tumor arose from the left labium minus by a wide pedicle. It completely filled the vagina, with a large amount of tumor protruding outside. The urethra was displaced upward, forward and to the right and was markedly angulated. There was an extension of the tumor over the left side of the mons pubis. The tumor and its extension were completely excised. The upper portion appeared to be encapsulated, but the intravaginal portion deeply infiltrated the vaginal wall. The resulting defect was closed with sutures of surgical gut U. S. P.

Examination of the mass revealed a lobulated, friable, reddish gray tumor, weighing 508 Gm. Microscopically, it proved to be a typical fibromyxosarcoma of only a moderately high degree of malignancy.

Convalescence was complicated with the appearance of generalized edema and persistent tachycardia, which were controlled by the administration of digitalis U. S. P. The wound healed per primam. The patient was dismissed from the hospital on the fourteenth postoperative day. She was able to walk with slight assistance.

She was readmitted on June 29 with acute retention due to a urethral stricture; this responded satisfactorily to dilation. She was next admitted on November 22 with bilateral enlargement of the inguinal lymph nodes. There was no evidence of local recurrence or of distant metastasis. Radical dissection of the inguinal lymph nodes was carried out. Microscopic examination revealed a small area of sarcoma in only one node. This area resembled the original tumor, except that it was somewhat more cellular.

THE PATHOGENESIS OF TUBERCULOUS EPIDIDYMITIS. WALTER M. BORTHWICK, Edinburgh M. J. **53**:55 (Feb.) 1946.

The author presented this work as a thesis to the University of Glasgow and received commendation therefor.

Case records for twenty-one years showed 5,476 cases of tuberculosis in male patients, in 402 of which the histories revealed tuberculous involvement of the epididymis. The youngest patient was 8 months of age; the oldest, 63 years. Among the children there were 12 cases in the group up to 5 years of age, 4 in the group from 6 to 10 years of age and 12 in the group from 11 to 15 years of age, or 28 cases of the disease in children in the total of 402 cases. The figures for all ages bear out the evidence that genital tuberculosis in men is commonest in the years of maximal sexual activity. Injury was not of much influence in the production or localization of tuberculosis in these cases; gonococcic epididymitis was seldom, if ever, an influence in the occurrence of tuberculous epididymitis.

This thesis also includes descriptions of the local lesion, coincidental pelvic lesions and associated renal changes, as well as a discussion of the sequence of events in the pathogenesis of tuberculous epididymitis. **NEFF**, Kansas City, Mo.

EXTRACTIONAL HYPERGLYCEMIC PRINCIPLE FROM URINE OF HEALTHY CHILDREN. A. LIOTTA, Riv. di clin. pediat. **40**:300 (May) 1942.

From the urine of each of 15 children, 2 to 15 years of age, an extract was obtained, which when given intravenously to rabbits caused an increase in the blood sugar. The average rise was from a normal fasting value of 1.05 per cent to 2.50 per cent in five hours. The extract lost its potency after being kept in an ice box for one month.

HIGGINS, Boston.

Diseases of the Ductless Glands, Endocrinology

THE EFFECT OF PITUITARY ADRENOTROPIC HORMONE ON THE CHOLESTEROL AND ASCORBIC ACID CONTENT OF THE ADRENAL OF THE RAT AND THE GUINEA PIG. GEORGE SAYERS, MARION A. SAYERS, TSAN-YING LIANG and C. N. H. LONG, Endocrinology **38**:1 (Jan.) 1946.

The injection into rats and guinea pigs of highly purified adrenotropic hormone of the anterior lobe of the pituitary gland is followed by a prompt fall in the ascorbic acid content and a slower fall in the cholesterol content of the adrenal glands. It is suggested that these changes in the ascorbic acid and cholesterol contents of the adrenal gland under the influence of the adrenotropic hormone are associated with the formation and release of the hormones of the adrenal cortex.

JACOBSEN, Buffalo.

THE INFLUENCE OF DIETHYLSTILBESTROL ON ALLOXAN DIABETES PAIRED FEEDING EXPERIMENTS. R. H. JANES and H. DAWSON, Endocrinology **38**:10 (Jan.) 1946.

From the data presented, it is not apparent that diethylstilbestrol U. S. P. is a diabetogenic agent or that it ameliorates diabetic symptoms in the rat.

JACOBSEN, Buffalo.

THE INFLUENCE OF ADRENALECTOMY ON THE UTILIZATION OF ACETONE BODIES. EATON M. MACKAY, ARNE N. WICK and CYRUS BARNUM, Endocrinology **38**:30 (Jan.) 1946.

Adrenalectomy produces an increase in the rate of utilization of acetone bodies in the fasting rat with ketosis. It is suggested that the deficiency in available glucose in this condition is responsible for the increased ketolysis.

JACOBSEN, Buffalo.

ESTROGEN INACTIVATION AND FOLIC ACID. OSCAR KOREF and PAUL ENGEL, Endocrinology **38**:133 (Feb.) 1946.

Folic acid (pteridyl-para-aminobenzoyl glutamic acid) in relatively high amounts inhibits the estrogenic activity of estrone U. S. P. (theelin) to a certain, rather moderate degree. One milligram of folic acid inactivates almost 50 international units of estrone. Folic acid is certainly not the substance responsible for the vigorous estrogen-inactivating potency of liver in vitro.

JACOBSEN, Buffalo.

CONGENITAL ADRENAL CORTICAL INSUFFICIENCY ASSOCIATED WITH MACROGENITOSOMIA: FOLLOW-UP AND TERMINAL REPORT. H. E. THELANDER, J. Pediat. **29**:213 (Aug.) 1946.

A case of congenital insufficiency of the adrenal cortex (Addison's disease) in a boy was followed for six years to the time of his death with measles and convulsions. The child showed the associated syndrome of overproduction of the androgenic hormone, resulting in accelerated growth and precocious sexual development. At 6 years of age he weighed 88 pounds (39.9 Kg.) and was 57½ inches (146 cm.) tall. His bone age at 14 months was that of 3 years, at 24 months that of 6 years, at 36 months that of 8 to 9 years and at 5 years, the last bone age taken, it was 11 years. He had the configuration of an adolescent child, with the enlarged larynx, bass voice and hair distribution of his physiologic age. His penis was of adolescent size, but his testes were small. He had no 6 year molars and had lost only his front incisors. His intelligence quotient was 110.

The deficiency of adrenal cortex was adequately made up through the use of desoxycorticosterone acetate sublingually, 16 to 20 drops daily in divided doses of 4 to 5 drops each.

He tolerated without undue severity exanthema subitum, pneumonia, tonsillitis, chickenpox and a tonsillectomy and adenoidectomy. With his attack of measles convulsions quickly developed, and he remained unconscious with intermittent convulsive seizures until death occurred.

The autopsy revealed the characteristic pathologic changes of this disease, namely, bilateral hyperplasia of the adrenal cortex, which was extreme; aberrant adrenal cortical rests in both testis; macrogenitosomia with pubertas precox, adult body contour and hyperplasia of the prostate; persistent thymus; hypertrophy of the juxtaglomerular apparatus, and the usual pathologic lesions of measles.

The cause of this condition is not known. FROM THE AUTHOR'S SUMMARY.

Diseases of the Muscles, Bones, Joints and Lymph Glands

JUVENILE RHEUMATOID ARTHRITIS: A STUDY OF FIFTY-SIX CASES WITH A NOTE ON SKELETAL CHANGES. JAMES A. COSS JR. and RALPH H. BOOTS, J. Pediat. **29**:143 (Aug.) 1946.

A study was made of 56 patients with juvenile rheumatoid arthritis. This series represents 4.9 per cent of all persons with rheumatoid arthritis seen in the clinic or wards of the Columbia Presbyterian Medical Center. The term "Still's disease" is avoided as it suggests an artificial distinction between arthritis in children and arthritis in adults. In this series, the age at onset of the disease was 12 years or less. The distribution according to sex of 5 female patients to 1 male patient is the same as in adults. Splenomegaly, hepatomegaly and glandular enlargement may occur at any age.

Eighteen patients (32 per cent) had a family history of arthritis, rheumatic fever or related illness. Thirty-two patients (57 per cent) gave a history of aural or nasal infection or of infection of the respiratory tract preceding or associated with the onset of arthritis. Thirty-nine patients (69 per cent) gave a history of such infections during their illness.

There was anemia in 80 per cent of these patients and leukocytosis (over 25,000 cells) in 17 per cent of them. High leukocyte counts are often associated with a poor prognosis. Hemolytic streptococci were cultured from the throat in 60 per cent of those patients tested.

The differentiation between rheumatic fever and juvenile rheumatoid arthritis is often difficult. The response to salicylates is helpful, as it usually appears more promptly in rheumatic fever. Certain laboratory tests were of little value in distinguishing juvenile arthritis. The titer of antistreptolysin O is significantly elevated just as in rheumatic fever. As in rheumatic fever, there is rarely a positive reaction to the streptococcus agglutination test. Negative reactions do not become positive as the age of the patient increases. Changes in the electrocardiogram occur in both conditions. Myocardial damage or carditis were discovered in 7 of the patients in this study on electrocardiograms. On follow-up studies of 6 of these patients, the patterns reverted to normal. Forty-seven per cent of patients showed some cardiac deviation, varying from persistent tachycardia in 13 per cent to the aforementioned electrocardiographic changes.

Twenty-two patients received chrysotherapy; there were 2 instances of moderate toxicity. Therapy with gold compounds is no more dangerous in children than in adults.

Certain skeletal changes, cervical fusion, cervical luxation and brachydactylia, which were not previously related to rheumatoid arthritis, are described. The characteristic birdlike facies is considered to be the effect of arthritis on the mandible.

Reports on typical patients are presented, including the 2 who died. One of these children was shown to have amyloidosis. Roentgenograms and photographs illustrate the skeletal changes.

FROM THE AUTHORS' SUMMARY.

OSTEODYSTROPHY IN A GIRL: AN UNUSUAL CASE. A. GALEOTTI FLORI, Riv. di clin. pediat. **40**:257 (May) 1942.

The author's patient, a girl, had shown alterations in the bones of the fingers from the age of 7 years. All the phalanges, especially the distal ones, showed slow growth, irregular development and hypercalcification at the epiphyses and diaphyses. There were similar but less pronounced changes in the great trochanters, the bones of the elbow joint and at the junction of the ischium and the pubic bones.

HIGGINS, Boston.

NONSPECIFIC SPONDYLITIS. H. WISSLER, Helvet. pædiat. acta **1**:451 (Oct.) 1946.

Four cases of nonspecific, subacute or chronic spondylitis in which the diagnosis of tuberculosis was made are presented. In 1 case osteomyelitis of the leg below the knee eleven years previously was the possible cause; in the others the etiologic factor was unknown. The differential diagnosis of this disease from spondylitis tuberculosa is discussed.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Eye

CONGENITAL CATARACTS IN SISTERS WITH CONGENITAL ECTODERMAL DYSPLASIA. H. N. COLE, HORACE K. GIFFEN, J. T. SIMMONS and GEORGE M. STROUD III, J. A. M. A. **129**:723 (Nov. 10) 1945.

"Two sisters had congenital cataracts of the lamellar type, extreme internal strabismus, hypoplasia of the nails, almost complete alopecia, atrophic nasal mucosae and a generalized hypoplasia of the skin. Both children stand heat poorly, both children are subnormal mentally and the older has dental hypoplasia. Microscopically there is an irregular hypoplasia of the skin and accessory structures, sweat and sebaceous glands and hair. In places all three are completely absent.

"Involvement of all ectodermal elements as seen in these sisters is very rare if not unique, and the picture presented approaches closely to that of congenital ectodermal dysplasia of the anhidrotic type but perhaps would better be classified as a combined ectodermal dysplasia.

"The dysplasia of ectodermal elements—with only a suggestive dental abnormality in the father and no other family history is probably 'incomplete dominant' in type."

AUTHORS' SUMMARY.

BAIRD, Wauwatosa, Wis.

TRACHOMA IN WEST AFRICAN NEGROES. J. G. SCOTT, Brit. J. Ophth. **29**:244 (May) 1945.

The purpose of this paper is to assess the rate of infection among Negroes in British West Africa and to describe the disease as it affects the natives.

Trachoma of the West Coast African Negro is a mild disease. It is of the general infiltrative type. It affects 5 per cent of school children, 10 per cent of soldiers and 25 per cent of population in some villages in the Gambia. The same disease is found in 10 per cent of soldiers on the Gold Coast, in 10 per cent of Nigerian soldiers and in 2 per cent of Cameroon soldiers. Three hundred American Negro soldiers had no similar infection but were not immune.

W. ZENTMAYER. [ARCH. OPHTH.]

CONGENITAL PARALYSIS OF THE EXTERNAL RECTUS MUSCLE (DUANE'S SYNDROME). C. PAIVA, Rev. brasil. de oftal. **3**:25 (Sept.) 1944.

This rare anomaly was first described in 1905 by Duane and is characterized by lessening or absence of external rotation of one or both eyes. It is caused by paralysis, usually partial, of the external rectus muscle and paresis of the internal rectus muscle, associated with a variable degree of retrocession of the globe and narrowing of the palpebral fissure during the movements of adduction or abduction. The patient shows no diplopia when looking straight ahead, although in some cases the head is turned slightly to the opposite side (ocular torticollis).

The clinical picture varies exceedingly, as can be seen from Adrogue's classification, presented in 1926. However, one symptom which characterizes this anomaly is present in every case, and that is the deficiency or congenital absence of abduction.

The cause is controversial. Some authors believe that the anomaly is due to the congenital absence of the external rectus muscle; others oppose this theory on the grounds that the lesion of the external rectus is always partial, while aplasia of the external rectus can be present without the enophthalmos which is always noted in cases of Duane's syndrome.

Diagnosis is made on the basis of objective and subjective data and of the anamnesis. The condition is easily diagnosed in the cases of unilateral retraction but is difficult to distinguish from a fixed alternating strabismus when it is bilateral. Differential diagnosis should be made between Duane's syndrome and functional strabismus or acquired paralytic strabismus of the sixth pair of cranial nerves.

Surgical treatment of this anomaly has been attempted but is generally unsuccessful. Some authors believe that an operation should be performed only when strabismus is present, and only then for the cosmetic effect.

The author presents one personal observation. A bibliography is included.

M. E. Alvaro. [Arch. Ophth.]

Pupillotonia (Syndrome of Adie) in an Imbecilic Child. M. Schachter, Ann. pædiat. **167**:135 (Sept.) 1946.

Pupillotonia, the syndrome of Adie, is rare in children. A case in a boy 8 years of age, with a rigid right pupil without anomalies of reflexes or without other symptoms of changes in the nervous system indicating syphilis, is reported. The child is an imbecile. A discussion of the symptoms, cause and pathogenesis of Adie's syndrome is included.

From the Author's Abstract.

Skin Diseases; Allergy

The Treatment of Scabies in Children with a New Sarcopticide. T. J. McElhenney, J. Pediat. **29**:189 (Aug.) 1946.

A series of 22 cases of scabies treated with an ointment containing "zyclophen" (a mixture of equal parts by weight of 4-chloro-3, 5-dimethylphenyl hydrogen *dl*-camphorate and ortho-phenylphenol) is presented. As result of his clinical observations, the author concludes that an extremely simple, apparently nonirritating and nonpainful agent, surpassing in effectiveness the usual antiscabietic preparations, is available in this sarcopticide. The treatment is described as particularly effective against the secondary pustular eruptions, and it is capable of bringing about complete and rapid cure through topical application, without complicated adjunctive precautions. The chemical formula of the active ingredient and a prescription for a suitable ointment are included.

Grulee Jr., Minneapolis.

The Treatment of Some Common Dermatoses of Infancy and Childhood. James W. Burks Jr., New Orleans M. & S. J. **99**:1 (July) 1946.

The author stresses the fact that effective treatment of dermatologic conditions in children depends on correct diagnosis. Oily skin can stand frequent watering; ichthyotic skin requires oil; seborrheic skin tolerates frequent bathing. Delicate skins may require colloidal baths or baths with a mixture of equal parts of solution of calcium hydroxide U. S. P. and olive oil.

For edematous, erythematous and exudative eruptions, wet dressings are helpful. As the eruption subsides, ointment of calamine or boric acid may be used. For pruritus, menthol and phenol are added to the mixture of solution of calcium

hydroxide and olive oil. Sulfur and Peruvian balsam U. S. P. in petrolatum U. S. P. and hydrous wool fat U. S. P. are advised for scabies. Ammoniated mercury U. S. P. leads the author's list for use in treatment of impetigo. In dermatitis venenata he advises application of a 0.5 per cent solution of aluminum acetate and colloidal baths.

For those interested, formulas and details of treatment are given.

BERKELEY, Beverly Hills, Calif.

ACRODYNIA [ERYTHREDEMA POLYNEUROPATHY] PYRIDOXINE. G. FRONTALI, Arch. ital. di pediat. e puericol. **11**:3 (March) 1946.

The author presents a general exposition of the pathogenic and anatomicohistologic aspects of infantile acrodynia (erythredema polyneuropathy). He discusses his series of 10 cases from various points of view—clinical, pharmacodynamic and hemochemical and in relation to the metabolism, the pyridoxine content of the blood and urine, porphyrinuria and the effect on the capillaries of the body surface. A diet devised by the author increases the symptoms, while the administration of pyridoxine is followed by prompt recovery. No similar effect is obtained with the administration of any other known component of the vitamin B complex.

FROM THE AUTHOR'S ABSTRACT.

Surgery and Orthopedics

CONGENITAL DISLOCATION OF THE HIP. BURTON W. TRASK, Am. J. Roentgenol. **55**:299 (March) 1946.

A roentgenogram was made of the skeleton of a newborn infant who had a cutaneous depression at the level of the lumbosacral joint. The joint was reported to be within normal limits. One and one-half years later the patient was examined again and presented a definite dislocation of the right hip. In a review of the original roentgenogram it was shown that the right femur was slightly farther from the pelvis than was the left femur. This case demonstrates that a dislocation can be present in the neonatal period without the presence of all the mechanical factors.

HARRISON, Chicago.

Teeth and Dentistry

EPIDEMIOLOGIC STUDIES IN DENTAL CARIES: I. THE PATTERN OF DENTAL CARIES IN IOWA CITY CHILDREN. JULIAN D. BOYD and VIRGIL D. CHEYNE, J. Pediat. **29**:157 (Aug.) 1946.

The serial dental records of 60 boys and 41 girls were reviewed to determine the course of tooth decay in a presumably representative child population. The records were drawn from the files of the Children's Clinic of the College of Dentistry, Iowa City. Each child included in the study had been examined at least six times during not less than three years. At each visit to the clinic the necessary reparative dental therapy had been performed in a competent manner. Technics of examination and of recording were constant throughout the study.

Despite the recurren dental care, caries had progressed almost without exception. In 75 per cent of the children, the average annual increment of newly carious tooth surfaces was not less than 2.25, and the median value was 3.8 surfaces. In contrast to this evidence of progressive tooth destruction, during the course of study only one permanent tooth among all the children was lost because of decay.

Much individual variation was noted as to the progression of caries, not only among the subjects, but in the same child at different periods of observation. The children with the least amount of caries at the initial examination showed greater inconstancy in the pattern of subsequent caries than did those with a high initial incidence of caries. Those children initially in the interquartile zone showed a greater tendency to remain in that position than to shift to another quartile rank.

The nature of the study did not permit much analysis of factors which might have contributed to the variability in dental response. Most of the subjects had always lived in Iowa City, where the drinking water does not contain a significant amount of fluorine.

Practically, it may be concluded that recurrent dental therapy does not, of itself, prevent the development of tooth decay. However, the low incidence of tooth loss speaks for the protective effect of reparative dental treatment.

From the viewpoint of dental research, the study emphasized the unreliability of data based on short term periods of observations as evidence of the efficacy or inefficiency of specific agents affecting the incidence of caries. The data indicate that it may be more profitable to employ as experimental subjects those children whose incidence of caries in the past places them in the median group than to choose a random sample of subjects without regard for their earlier course of tooth decay.

FROM THE AUTHORS' SUMMARY.

Miscellaneous

A MODIFICATION OF THE BRECHT FEEDER. JEAN G. HESS, J. Pediat. **29**:233 (Aug.) 1946.

A description is given in this article of a slight modification in the Brecht feeder which may prove of value.

EDITOR'S REVIEW.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

Harold K. Faber, M.D., *President*

Fifty-Seventh Annual Meeting, Stockbridge, Mass., May 13-15, 1947

President's Address: Causes and Possibilities of Prevention of Cerebral Damage to Infants and Children. Dr. Harold K. Faber, San Francisco.

Acute Gastroenteritis in a Children's Summer Camp Due Apparently to a Paracolon Bacillus. Dr. T. F. McNair Scott, Dr. H. J. Davis, Dr. L. L. Coriell and Dr. Ben H. Boltjes, Philadelphia.

In a group at a children's summer camp, consisting of 222 children and 81 adults of both sexes, an outbreak of gastroenteritis occurred involving 146 persons, or 48 per cent. Epidemiologic evidence pointed to beef as being the vehicle of infection. On this hypothesis, the incubation period was for the most part twelve to fifteen hours. The disease was mild, with a minimum of gastric symptoms, and was short lived, being over within thirty-six hours. The picture suggested a bacterial rather than a toxic type of food poisoning.

At the end of the epidemic, rectal swabs were taken from 43 persons, including 2 food handlers, who had had symptoms, and 10 food handlers who denied symptoms. None of the usual intestinal pathogens were isolated. From 12 of the persons with symptoms, organisms of the Paracolobactrum group were isolated, but none from asymptomatic food handlers. Two weeks later, after an interval free from diarrhea, a resurvey of 26 of the original patients, 33 controls and 9 food handlers yielded 10 organisms of this group.

Biochemical analysis of organisms isolated in the first survey revealed that 7 were Paracolobactrum intermedium, 4 P. aerogenoides (1 somewhat different) and 1 biochemically distinct. In the second survey, none of them were characteristic of these groups. Nine of the 10 organisms resembled P. coliforme, but all were closely allied to Proteus. Serologic analysis by direct agglutination and cross absorption tests revealed an antigenic relation among 11 of 12 organisms of the first survey, but none between these and organisms obtained on the second survey. The 11 related organisms formed 4 serologic groups: 1 in group 1 with wide antigenic crossing with the other groups; 2 in group 2, 7 in group 3 and 1 in group 4. All groups were agglutinated by Stuart's 32011 pooled antiserum. Convalescent serum agglutinated these organisms, but control serums did also, as did serums from children in a different community who were more than 6 months of age, but from none younger. These were probably natural antibodies, or they resulted from wide exposure to these organisms. The presence of an interrelated group of Paracolobactrum in 60 per cent of organisms isolated during an outbreak of gastroenteritis and not at another time is highly suggestive of a causal relation.

DISCUSSION

Dr. Hattie E. Alexander, New York: I should like to ask Dr. Scott whether the stools were examined microscopically for pus. In almost every instance of well established bacterial enteritis, it is possible in the majority of those patients with severe diarrhea to demonstrate pus microscopically.

Dr. T. F. McNair Scott, Philadelphia: We did not examine all the stools microscopically; we did examine one or two, and they contained no pus.

Familial Epidemiology of Hemophilus Influenzae, Type B, Infections. Dr. Paul L. Boisvert, New Haven, Conn.

I have been interested in infections caused by Hemophilus influenzae, type B, since 1939. It happened that about the time these infections began to be seen more frequently in New Haven, Dr. Hattie E. Alexander developed an effective rabbit serum. So I began to see a number of patients who could actually be benefited.

Family studies on this organism beginning in 1941 stemmed from earlier studies on hemolytic streptococcic disease and were carried out to protect the young siblings of a known patient. It is a well established fact that babies under 6 months of age who have the infection get along worse than older infants and children with the infection. The original plan was to make cultures of material from the nose and throat of the rest of the patient's family. If the cultures should yield no organisms, the parents could be assured that a treated sick child is never permitted to go home with a culture yielding organisms capable of reinfecting the family. Somewhat similar results could have been obtained on purely clinical grounds by determination of the incidence of secondary cases in a group of families. This method, however, would not show how the organism spread in a family.

Cultures of material from the nose and throat were made from the parents of the 52 families at the time of the sick child's admission and the material from the remainder of the family was cultured the following day (a total of 397 persons). It was originally planned that cultures be repeated at weekly intervals until all family members had two nose and throat cultures which did not yield the organism. Later in the study, cultures were taken monthly for convenience when it was discovered that 1 or more members of some families continued to harbor the organism for years. It was appreciated that a single culture yielding no organisms might not indicate absence of the organism from the rhinopharynx. The results of cultures from hospitalized patients did not support this observation, but conceivably so-called healthy carriers might harbor fewer type B influenza bacilli. Dr. G. W. Rake observed that persons might have several throat cultures yielding no meningococci before one yielding meningococci of the same type appeared.

The results of the study may be summarized as follows:

1. Infections caused by H. influenzae, type B, were numerically important and appeared from hospital data to be on the increase. Some of the increase could be explained by improvement in bacteriologic technic and by the system of referral of patients to New Haven Hospital for treatment. However, cultures of blood and spinal fluid always were routinely made, and examples of all types of meningitis always were referred to the New Haven Hospital for treatment. The Connecticut Department of Health cannot prove or disprove this evidence since cases of infection with influenza bacillus are classified as influenza along with the virus infections.

2. The organism can almost surely be recovered from the members of the family of a child hospitalized with a severe type B infection. Children are more likely to carry the bacillus than adults, with the exception of the mother who is as likely to be a carrier as a brother or sister and is eight times as likely to be a carrier as the father or other adult members of the family.

3. The duration of the carrier state is not known. The larger the family the more likely the members are to pass it back and forth.

4. Serious disease is unusual in children. There were 2 examples of secondary infection in this series, both of acute laryngitis.

5. The presence of H. influenzae, type B, in the nasopharynx is related to what may be described as the "common cold." This relation has statistical significance. In this connection, a 2½ year old boy was admitted with meningitis,

from which he died. His brother had died one year previously with the same disease. It is probable that he was exposed during his brother's illness, but proof was lacking, since these cases antedated the family studies.

6. Sulfonamide drugs were not used for prophylaxis because of low incidence of secondary serious disease in the family and because of fear of development of sulfonamide-fast strains so that one less drug would be available for treatment if a carrier should subsequently become seriously ill.

7. The organism has not been seen in nonfamilial playmates except in studies of schools and other institutions. However, it must be spread by this means. Also, no pooling of clinical conditions, such as bacteremia or meningitis, was observed in a particular section of the city.

8. Dr. Alexander's rabbit serum was used prophylactically in a family of 5 persons. Twenty-five milligrams of antibody N was given to each member, with elimination of the carrier state after one week. This disappearance might be significant or due to chance. The cost of the rabbit serum is now $40 per vial which restricts its use prophylactically at present, except on an experimental basis.

DISCUSSION

DR CHARLES A. JANEWAY, Boston: I wonder whether Dr. Boisvert has any data on the relation of the carrier state to immunity. If persons carry these organisms for such long periods, do antibodies develop during that time?

DR. JOHN A. V. DAVIES, Boston: I should like to add this: Some years ago when my colleagues and I were routinely typing pneumonias, Dr. Winthrop Franke, in our clinic, studied carriers of the type XIV pneumococcus in the families of children coming into the hospital with type XIV pneumococcus pneumonia. He did not publish his results, but they were strikingly similar to those of Dr. Boisvert.

DR. PAUL L. BOISVERT, New Haven, Conn.: I cannot answer the question about immunity developing in the carriers, because the incidence of severe disease is so low. I suggested that the 2½ year old boy mentioned in the paper may have acquired the organism from his brother when the brother was sick a year before. The patient was admitted with meningitis. I suppose that carriers may be immune because of the rarity of the disease in adults. Dr. F. G. Blake, of the medical service of this hospital, has about twice as many admissions per year, and no examples of the disease have been seen during the past ten years.

Mode of Action of Streptomycin on Type B Hemophilus Influenzae. DR. HATTIE E. ALEXANDER, New York.

Streptomycin when used alone in the treatment of Hemophilus influenzae meningitis resulted in prompt recovery when the infection was mild or of average severity. However, when the infection was severe, the results were disappointing; the chief cause of failure appeared to be the development of resistance of the organisms to streptomycin. In an attempt to obtain a better understanding of the mechanisms responsible and to prevent the occurrence of failure three aspects of the mode of action of streptomycin were explored: (1) character of the effect of streptomycin on sensitive organisms, (2) origin of the resistant organisms, and (3) nature of the resistant variants. The experimental results supported the following conclusions:

1. Streptomycin exerts a bactericidal effect on the sensitive members in the population.

2. The emergence of resistance of a strain during treatment of a patient with streptomycin represents a selective process; the sensitive members of the popula-

tion are rapidly killed, permitting the resistant variants, present in all sensitive strains, to declare their presence. Examination of enormous populations of ten strains showed that in each one prior to exposure to streptomycin, a small fraction of organisms is present which can thrive in the presence of 1,000 units of streptomycin per cubic centimeter. The prevalence has varied from 1 in 1,000,000,000 to 1 in 46,000,000,000.

3. These resistant variants, present in all large populations of the ten strains examined, possess characteristics of bacterial mutants.

A. Independent cultures of the same strain on different occasions and even cultures seeded in a single test with the same inoculum, showed decided variation in prevalence of resistant variants in populations of comparable size. This variation is just as great in genetically homogeneous culture sources as in the heterogeneous sources. Evidence is presented for the continuous random occurrence of these resistant variants.

B. The rate of occurrence of the resistant members is not significantly different for the ten strains studied; it varied from 2.6×10^{-11} to 7.0×10^{-11} per organism per bacterial generation. The results of 5 different tests on the same strain showed comparable variation, 2.2×10^{-11} to 7.5×10^{-11}. Therefore, emergence of resistance in three of these strains during treatment with streptomycin of the patient harboring them cannot be explained by their higher mutation rate. This low rate is consistent with the mutation theory.

C. Variants exhibiting resistance to 1,000 units of streptomycin per cubic centimeter transmitted this trait unchanged in degree through many generations. The results suggest that in a portion of the colonies resistant to strepomycin, an additional trait, differing from the parent culture, is associated; the nutritional requirements of these cultures are different.

DISCUSSION

DR. A. ASHLEY WEECH, Cincinnati: I should like to ask Dr. Alexander whether she has had any experience with the susceptibility of H. influenzae to penicillin. From statements in the literature my colleagues and I in Cincinnati had been led to believe that penicillin could be used in pharyngeal cultures to inhibit the growth of other organisms and to allow H. influenzae to be grown in pure culture. We have therefore been surprised to find that the majority of type B strains now being recovered from patients with meningitis are just as susceptible to penicillin as they are to streptomycin. I wonder whether experience has been the same in other places.

DR. HORACE L. HODES, Baltimore: My colleagues and I observed that each of twelve strains of H. influenzae isolated from patients with meningitis was more susceptible to penicillin than to streptomycin. Has Dr. Alexander's experience during the past winter been similar?

DR. FRANCIS F. SCHWENTKER, Baltimore: In this problem of whether the development of resistance to chemotherapy was due to mutation or to selective survival of various daughter organisms, I have been in favor of selective survival. I think the time has come that I have to admit that all the evidence seems to be in favor of mutation. I have been extremely interested in the reports of Miller's work at the University of Chicago on the meningococcus. Not only did some of his strains become resistant to antibiotic substances, but at least one strain developed as a mutation will not grow in the test tube unless the antibiotic substance is provided for it.

DR. HOWARD H. MASON, New York: Was it a sulfonamide drug which was used in the study on the meningococcus?

DR. HATTIE E. ALEXANDER, New York: I am glad Dr. Hodes answered Dr. Weech's question. He has had much experience in that field, and I have had little. Through an error in dilution, when penicillin was incorporated in blood agar for purposes of inhibiting other organisms, I demonstrated that H. influenzae is completely inhibited in a concentration of 2 units per cubic centimeter.

I should like to ask Dr. Hodes what range of sensitivity to penicillin he observed for a representative number of strains of H. influenzae. It is of interest that 1 unit of penicillin is equivalent to about 10 units of streptomycin. Also, I wonder whether there is evidence to show that penicillin, like streptomycin, is bactericidal for H. influenzae.

Dr. Miller demonstrated that some strains of meningococci which are resistant to high concentrations of streptomycin exhibit characteristics of strains 3, 7 and 10, showing change in their nutritional requirements. Moreover, such strains lose their pathogenicity for mice unless penicillin is added. We have not tested the pathogenicity of strains 3, 7 and 10, but several strains resistant to a concentration of 1,000 units per cubic centimeter retained their virulence.

DR. HORACE L. HODES, Baltimore: The sensitivity of the twelve strains ranged from just under 0.1 microgram for penicillin up to about 3 micrograms. It is interesting to note that in England at least 6 patients with H. influenzae meningitis were treated with penicillin and with sulfonamide compounds. I have a reprint of a report by a physician in Leeds, England, who treated 4 patients, 2 of whom recovered. I think the 2 patients who recovered were young children. There are other reports in the English literature of similar nature. I cannot answer the question concerning bactericidal properties completely except to say that for some of the strains we have tested penicillin appears to be bactericidal.

From a practical standpoint, we have wondered whether it would not be wise to begin treatment first with a short course of streptomycin in all cases, but to change to penicillin if prompt improvement does not occur.

DR. HATTIE E. ALEXANDER, New York: It is of great therapeutic importance that the resistant mutants have been shown to be sensitive to sulfadiazine. Therefore, the majority of patients with influenzal meningitis will probably be cured by the combined action of streptomycin and sulfadiazine.

DR. HOWARD H. MASON, New York: I am confused at this point, Dr. Alexander, because Dr. Schwentker has said the strains had to have sulfonamide compounds to grow; you said penicillin, and I understood from another report that it was streptomycin.

Streptomycin in the Treatment of Miliary Tuberculosis: Report of a Case.

DR. JOHN D. LYTTLE and DR. ELVIRA GOETTSCH, New York, and DR. GEORGE COBLEY, Los Angeles.

Two patients with miliary tuberculosis were treated with streptomycin. The first was an infant 11 months old for whom diagnosis was confirmed by biopsy of a lymph node, and the second was a child 3½ years old whose gastric washings produced Mycobacterium tuberculosis. Physical examination revealed no evidence of meningeal irritation in either patient, and the cerebrospinal fluids were normal on repeated examinations. One gram of streptomycin daily in divided doses was administered intramuscularly for three months. After this treatment both children were free from symptoms and the roentgenograms of the lungs showed complete

regression of the miliary lesions. Four and a half months after treatment was terminated in the first case, the patient showed no symptoms suggestive of reactivation of tuberculosis. Two months after administration of streptomycin was discontinued, tonsillectomy and adenoidectomy were performed, and pathologic examination of the tonsillar tissue showed the typical morphologic evidence of tuberculosis. The second patient was free from symptoms one month after cessation of treatment.

DISCUSSION

DR. WARREN R. SISSON, Boston: Because of the paucity of material on this general subject of streptomycin for tuberculosis, I am going to show a few slides of a child whom Dr. Sidney Gellis, of Boston, and I treated recently. The infant girl, whom we observed since birth, at 6 months of age weighed 18 pounds (8.165 Gm.). Soon after, a fever developed which later was discovered to be due undoubtedly to a tuberculosis infection because of her allergic reactions to tuberculin and a definite history of exposure to an itinerant uncle whose sputum yielded organisms on culture. This child was under observation for two months and was treated with streptomycin. I can show briefly the progress of the disease. No conclusions, however, should be drawn from our results. They merely bring up the question of whether observations should not be pooled so that these infants may be treated more intelligently.

[Slide] This is a first picture of the child when she had tuberculosis, at about 7 months of age. At this time she was in the hospital for observation because of an unexplained elevation in temperature. Incidentally, she continued to have a high white blood cell count of 35,000 cells for many weeks. The slide shows the extreme involvement of the hilus.

[Slide] The second slide, by means of a barium shadow, shows the infringement of the lymph nodes on the esophagus.

[Slide] After the child had been observed for three or four weeks, it was decided to use streptomycin. She was given 1,000,000 units a day. This slide shows that the lesion was either perifocal or possibly of nontuberculous origin.

[Slide] This roentgenogram was taken about a week after streptomycin therapy had been substituted. It shows that the prominent lesion, which you just noticed, has practically disappeared, although the shadows on the hilus are practically the same.

[Slide] This slide was taken last week. It shows a questionable perifocal lesion, and possibly some narrowing of the hilar lesion.

[Slide] This diagram is a brief summary showing the period of treatment with streptomycin which was given in doses of 1,000,000 units per day for one month, then in doses of 750,000 units for one month. It also shows the temperature record which has gradually become normal during the past ten days or two weeks. The child's weight dropped from 18 to 14 pounds (6,350 Gm.). Symptomatically, she is a great deal improved, although her weight remains stationary. Some sedimentation rates were high, but a recent one has not been reported.

The question arises as to whether this child was actually benefited by this treatment or whether she would have improved without such expensive therapy. The only question in my mind is whether or not, temporarily, we have prevented some of the secondary or the perifocal lesions from extending into a major and lethal form of the disease.

DR. JULIAN D. BOYD, Iowa City: Certain instances of primary tuberculous disease of the lung are easily confused with miliary tuberculosis on the basis of the

roentgenogram of the chest. The spontaneous recovery of such children regardless of therapy is to be expected. The following patient's record serves as an example.

In December 1929 a 16 month old girl came to the hospital with her mother. The mother had far advanced pulmonary tuberculosis and died six weeks after reaching the hospital. The child was apparently well, but roentgenograms of the chest revealed diffuse mottling of both pulmonary fields, and the pictures were interpreted by the roentgenologist as representative of miliary tuberculosis. The child remained in the hospital for the next seven months. Roentgenograms were obtained at two week intervals, and repeatedly they were interpreted as showing typical miliary tuberculosis. Stomach washings were positive for tubercle bacilli by the guinea pig inoculation test, as was fluid removed from a swollen knee in April. Despite the pulmonary signs the child was free from fever or symptoms of illness other than the swollen knee previously mentioned. The involvement of the knee subsided after a single aspiration. The child gained weight consistently throughout her stay in the hospital.

In March 1930, a distinguished foreign pediatrician, Dr. von Groer, of Poland, visited the pediatric department and saw this patient. My colleagues and I expressed our astonishment at such favorable progress in a child with miliary tuberculosis. He pointed out in the roentgenograms that the parenchyma of the lung was not uniformly or completely involved as one would expect if the infection were hematogenous in its distribution. He expressed the belief that the condition was one of primary tuberculous infection with multiple areas of involvement. The clinical course of the patient supported his conclusion. At her discharge from the hospital in July, the roentgenograms of the chest showed but slight evidence of opacity in three different areas, each of which one may interpret as the site of a primary infection which initially was so diffuse that it appeared to involve the whole pulmonary field.

DR. CHARLES F. MCKHANN JR., Cleveland: Probably every one present has had some experience with streptomycin, and in order to pool the experience, could we have a showing of hands? How many have treated miliary tuberculosis or tuberculous meningitis with streptomycin? (Forty-three hands were raised, according to Dr. H. G. Poncher, of Chicago.) Then, 43 persons in this room have had experience in treating tuberculosis, either the miliary or meningitic form, with streptomycin. How many have seen apparent cures from this treatment? (Sixteen hands were raised.) How many are satisfied that they have seen gross failures? (Twenty-six hands were raised.)

I think it is important to summarize our observations in this manner. It is obvious that streptomycin in some instances arrests or cures tuberculosis. Studies on experimental animals proved beyond any doubt that in a majority of instances streptomycin will arrest tuberculosis.

The same thing can be achieved by the use of certain chemotherapeutic agents, sulfone compounds, for example, and my associates and I at present have a few cases with apparent cure in which we used the combination of streptomycin and sulfone agent, such as "promin" (sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) or "promizole" (4,2′-diamophenyl-5′-thiazolylsulfone). Experimental evidence suggests that the two drugs, each of which has some effect, when used together may do somewhat more (Smith, M. I.; McClosky, W. T.; Jackson, E. L., and Bauer, H.: *Proc. Soc. Exper. Biol. & Med.* **64**:261 [Feb.] 1947). This cannot be stated as a proved clinical observation, but it is highly suggestive. If something can be achieved with each alone, perhaps the combination may be used

until a single more efficacious agent is obtained so that further additions may be made to the list of patients who apparently have been cured.

DR. HAROLD E. HARRISON, New York: I gathered from Dr. McKhann's final statements that he was discouraging us from the use of streptomycin, and I do not think such a conclusion should be drawn on the basis of present data. My colleagues and I treated 4 patients with miliary tuberculosis with streptomycin at the Baltimore city hospitals. In 2 patients under 1 year of age, there was no response whatsoever; the course of illness continued to go downhill, and the patients died in the usual time. In 2 other patients, however, one 6 years of age and 1 of 11, dramatic types of response occurred, which could not have been spontaneous remissions of the disease.

Both these children had meningitis. The disease in 1 was far advanced on admission, and meningitis developed in the other after ten days of intramuscular administration of streptomycin for miliary tuberculosis. In both children the meningitis cleared, or apparently cleared, after intrathecal treatment was started. I think the most significant reports will come from the accumulation of data on patients treated in the hospitals of the Veterans Administration.

We noticed one interesting phenomenon in the 2 children who apparently recovered; both these children had negative reactions to tuberculin at the time of admission, and, as they clinically improved, they became extraordinarily sensitive to tuberculin, much more so than the average patient. During this period of extreme sensitivity to tuberculin in 1 of the patients tuberculous uveitis developed which necessitated enucleation of the eye. It is likely that unusual complications may be seen in patients with miliary tuberculosis treated with streptomycin. Both patients in whom the disease was arrested have evidence of loss of vestibular function by the usual caloric tests, but show few or no symptoms relative to vestibular damage. It may be that these children are incapacitated for useful occupations because of this vestibular injury.

DR. GEORGE COBLEY, Los Angeles: I am gratified that our paper raised this discussion. I want to thank Dr. McKhann for obtaining a census of the group. We must admit that 16 cures is an excellent result and that it should encourage each of us to continue treatment of these patients.

We are treating 2 more patients at the Children's Hospital whose conditions are similar to the 2 reported on. It is too early to say what the results will be.

I do not believe we can call any of these patients cured. We must wait for the final answer.

I should like to know whether the patients that failed to respond to treatment had any meningeal involvement. We know the prognosis is much worse for these patients. I believe we probably will get better results once the dose and the length of treatment are standardized.

In answer to Dr. Boyd, I believe the diagnosis in these 2 cases is established beyond a doubt. I agree with Dr. Sisson that we ought to pool our knowledge and establish a common basis for treatment. In answer to Dr. Harrison, our patients compensated for their vestibular dysfunction without a trace of any disturbance in equilibrium remaining.

Encephalopathies Following Prophylactic Use of Pertussis Vaccine. DR. R. K. BYERS and DR. FREDERICK MOLL, Boston.

In common with many other biologic materials, pertussis vaccine used prophylactically is capable of producing an acute encephalopathy. At the present rate and

mode of use of the vaccine, such encephalopathy appears to occur about twice as frequently as that produced by the vaccination of the entire population against smallpox.

Nearly twice as many children were seen at this clinic with encephalopathy incident to whooping cough itself as were seen with encephalopathy following inoculation with pertussis vaccine. Of these children about one-half were under 7 months of age and, therefore, too young to have been saved by the use of vaccine.

Since an important risk of encephalopathy attends the use of pertusssis vaccine prophylactically, its universal administration is warranted only if it can be shown to be effective in the prevention of encephalopathy or death in large groups of children. If avoidance of the inconvenience of the average attack of whooping cough is all that is expected, the risk seems considerable. Whether modifications of the vaccine or new methods of administration will reduce its hazards remains to be seen.

DISCUSSION

DR. JOHN J. MILLER JR., San Francisco: This is an important and challenging paper. My colleagues and I have been using pertussis vaccine suspended or absorbed in isotonic solution of sodium chloride, straight or blended with toxoids, at Stanford Clinic for the past eleven years. Dr. H. K. Faber asked me to look up our incidence of convulsions. I was able to find file cards on more than 3,700 babies who completed the course of immunization. On two cards mention was made of convulsions within twenty-four hours subsequent to injections. One of these instances occurred last September (1946) after a primary injection of a mixture of toxoid and vaccine. We were able to recall the child to the clinic. He is normal mentally and physically. A family history of febrile convulsions was elicited in the mother and in the sister. Another instance occurred in 1940 following a third injection of vaccine in isotonic solution of sodium chloride. The child was subsequently seen in our clinic for two years. He was normal when last seen.

There appear to be three possible explanations of the encephalopathies which Dr. Byers described. The first explanation, and the most likely in my opinion, is that the vaccine injected contained Hemophilus pertussis endotoxin in large amounts. As Dr. Byers said, encephalitis has been produced in experimental animals with endotoxin. Dr. W. E. Ehrich, of Philadelphia, produced foci of encephalitis in rabbits by intravenous injections of toxic extracts of H. pertussis, as well as by massive injections of vaccine. Evans and Oddy, of England, have produced convulsions in rabbits, associated with hypoglycemia, by means of intravenous administration of endotoxin. In man the degenerative type of postpertussis encephalopathy occurring rarely in patients who do not have severe cough or convulsions was ascribed by Yamaoko to a neurotoxin, though other pathologists cited anoxemia as the prime factor. Interestingly, Thompson, who actually treated patients with whooping cough with endotoxin, noted that in some the injections aggravated the symptoms. Thus, there is considerable evidence that the endotoxin of H. pertussis is directly neurotoxic, or indirectly so, by damaging the capillaries.

The second possibility is that the persons afflicted had a constitutional tendency to convulsions, or even some cerebral damage before they were given vaccine. This explanation, however, is less likely.

The third possibility is that these children had a latent virus infection with herpes, or some other potentially neurotropic virus, which was activated by the vaccine in some way.

Dr. Byers collected 13 cases in Massachusetts, but, as far as we have been able to discover, no cases have been reported elsewhere. I have been informed that the two leading authorities on vaccination against pertussis, Dr. L. W. Sauer, of

Evanston, Ill., and Dr. Pearl Kendrick, of Grand Rapids, Mich., observed no cases of postvaccination encephalopathy. This geographic restriction I think is of great importance and might furnish a clue toward the solution of the problem.

I am glad to report that since March 15 of this year (1947) the National Institute of Health has recommended that H. pertussis vaccines be tested for toxicity before their release by the manufacturers. Should H. pertussis endotoxin be the responsible factor, such tests may be of the greatest importance.

DR. A. ASHLEY WEECH, Cincinnati: I am impressed by the figures presented by Dr. Byers. Because the conclusion, if correct, is of tremendous importance to American pediatrics, I am impelled to question its justification. To construct a statistical contingency table, one would have to know (1) the total number of persons in the community with encephalopathy, (2) the number of persons in the community without encephalopathy, (3) the number given pertussis vaccine, and (4) the number not given pertussis vaccine. Only when figures can be assigned to all four cells of the contingency table is it possible to calculate a value for χ^2 so as to determine whether or not the implication of the data is statistically reliable. Because the table is not complete, I am unhappy about the conclusion.

DR. CHARLES HENDEE SMITH, New York: I had in mind exactly Dr. Weech's point. Are we sure that in some of these children encephalopathies would not have developed without pertussis vaccine?

For many years I have been impressed by the difficulty of being sure that a child was absolutely normal in early infancy. I know of a number of children who were not suspected by obstetrician, pediatrician or parent of being abnormal until well along in the first year. Their condition then went on to so-called birth paralysis which was caused by either a birth injury or developmental factors. Moreover, in a certain number of children high fever develops after inoculations against pertussis. It is my custom to warn every parent that a febrile reaction is likely, and the mother is told to start giving acetylsalicylic acid as soon as the temperature starts rising. In that way it is possible to control the high temperatures. Most of the convulsions one sees from fever occur only when the temperature reaches 104 or 105 F. or more. I wonder whether control of the fever may not have some influence in prevention of these convulsions and, possibly, of subsequent real cerebral damage.

DR. DOUGLAS N. BUCHANAN, Chicago: I should like to support Dr. Byers' thesis. In Chicago my associates and I have seen a number of children who have responded to injections against pertussis by having convulsions. This response, however, has not been looked on as being unusual because no evidence of any specific connection between the convulsions and the injections existed. However, I know 3 children who live in Chicago who have been watched for about four years. All 3 children responded twenty-four hours after the first injection against pertussis with a mounting fever, and within forty-eight hours had sunk into complete coma. From that time they have remained in a condition of complete decerebration.

DR. R. CANNON ELEY, Boston: The suggestion of Dr. Miller relative to the geographic distribution of this complication seems pertinent. Various observers showed that in vaccination against smallpox the tendency to develop encephalitis appears more frequently among persons with a respiratory infection at the time of vaccination. Several theories, some fanciful and some practical, were offered as explanations for the development of encephalitis as a complication of measles, chickenpox and whooping cough, yet none of these theories seem wholly adequate. I think that the history of an acute infection of the respiratory tract at the time of

inoculation is important and that such an infection may have some influence on the development of untold reactions of the central nervous system. Allergic responses were also considered by some authors as the etiologic factor in encephalitis.

DR. SAMUEL KARELITZ, New York: I believe that cases of death due to anaphylactic shock following pertussis vaccine have been reported. I wonder whether some of these cases, especially those in which reaction occurred within twenty minutes after the injection are not likely to be cases of allergic reaction. Certainly, alteration in the central nervous system with dire consequences has been seen after the injection of vaccines made with horse serum. I recall a specific instance of antipneumococcic serum which resulted in the usual serum reaction, but a second injection given in error after a two week period resulted in a hemiplegia and coma. This child remained defective and paralyzed for years afterward and is in that state, as far as I know, at present.

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: I should like to ask Dr. Byers if an unusual degree of lymphocytosis occurred in his patients as a result of receiving the injection of vaccine.

Although there is no direct evidence for it, certain workers suspected that a toxin, perhaps derived from the organism, may have something to do with changes in the nervous system during pertussis.

Dr. V. B. Dolgopol, of New York, was of the opinion that the pathologic lesions of the brain observed in association with convulsions due to pertussis are most probably circulatory in origin, since ischemic cellular degeneration and plugs of lymphocytes in the small vessels are frequently seen. Since the heat-labile toxin can cause lymphocytosis and also necrosis of bronchial epithelium, it is logical to suspect that it might affect the brain.

I should also like to ask Dr. Byers if he assigns any significance to the fact that 12 of the 14 patients in his series were boys.

DR. EDWARD B. SHAW, San Francisco: Some children seem to react with a convulsive seizure to almost any febrile provocation; this is especially true of the child who has some injury to his central nervous system as an incident of birth or of the neonatal period. Damage which may finally be evident is ascribed often to later incidents rather than to the original cause of injury. Multiple neuropathies in the same person seem to me to be more frequent than can be accounted for by pure chance. In the same child poliomyelitis, postinfectious encephalomyelitis, meningitis and other conditions develop, suggesting especial vulnerability of the central nervous system. Mothers are prone to grasp at external injury, such as various forms of trauma, including immunizing injections, as the precipitating cause for mental subnormality, and, in the present series, the histories obtained from the parents might conceivably be misleading.

I should grasp at the hope that some especial vulnerability of the patient, perhaps occasioned by previous damage to the brain, might be responsible for the serious end results reported rather than the intensity of neural damage inflicted by the pertussis antigen. The relative infrequency of these encephalopathies due to pertussis vaccine seem to support such a view.

Various types of injury causing death have been reported as due to the injection of almost every type of particulate matter. Sometimes these injuries are caused by inadvertent intravenous injections, and sometimes they are doubtless due to embolism. Completely adventitious factors such as unrelated and coincident infection are occasionally responsible. There were, I think, 2 deaths recorded in Dr. T. Madsen's original series (1925) of children receiving pertussis vaccine, which

occurred in young infants. If the present series points to an especial hazard, it may apply particularly to immunization attempted extremely early in infancy.

Many of the pertussis vaccines are harvested from mediums containing human blood, and I should like to ask whether these particular vaccines, by analogy to the difficulties encountered with certain virus vaccines employing human blood serum, seem to have been especially productive of these neuropathies.

The conclusions of this study should be most thoughtfully examined, for it would be unfortunate if their implications were to impair a campaign which, nationwide, has tremendously reduced the incidence of whooping cough.

DR. HOWARD H. MASON, New York: Would those who have seen convulsions shortly after a child received pertussis vaccine, please raise their hands? [Twenty-five hands were raised.]

DR. KATHERINE DODD, Cincinnati: Were the convulsions febrile or were they indicative of real encephalopathy?

DR. HOWARD H. MASON, New York: How many want to bear out that they saw patients with encephalopathy? [Twelve hands were raised.]

DR. RANDOLPH K. BYERS, Boston: I am afraid I cannot answer all the questions, but I will try to do the best I can with some of them at least. In relation to Dr. Miller's remarks, he said something about the development of encephalopathies early in the course of whooping cough. One child in the series of 26 who had whooping cough and its encephalopathy came to the hospital primarily because of coma, convulsions and symptoms of encephalopathy. He had had no vaccine. He had at that time a high white blood cell count with lymphocytosis in the range of 80 per cent. Whooping cough developed in the next two weeks after he came to the hospital.

I never have understood that child's condition in relation to the pathologic development of whooping cough encephalopathy, which is said to be due to anoxia from the spasms of coughing.

Dr. Miller said I had collected 26 cases. It is not as bad as that. I collected 13 of encephalopathy following administration of pertussis vaccine. I tried to find out from the physicians who had given the vaccine whether it was their habit to pull back on the plunger of the syringe before injecting the vaccine. Two said it was, and as for the rest, the idea was new to them, I think.

Now, as to kinds of vaccine used in the series: all the different manufacturers' brands of vaccine I have ever heard of were included. As I understand it, some of them used human serum in their preparations, and some were using horse serum and washing the bacilli. The child who was vaccinated in 1937, I am sure, had that type of vaccine.

As to Dr. Weech's tables, I am afraid I have no idea how many children were vaccinated in Massachusetts, or how often this tragedy occurs. It must be an unusual one.

As to Dr. Smith's remarks, there were several children in this group who had been walking and talking, and who were known to be able and effective children before their vaccination. They had permanent neurologic damage and were changed from their previous situation after the vaccination. Many of the children were too young, of course, for one to be certain about their nervous system, but several who were 12 to 18 months old showed this change incontrovertibly.

As to Dr. Eley's suggestion about the presence of respiratory infection, I can make no statement. Many of these incidents were so far in the past that we have

no data on that point. The little child who had a fairly normal encephalogram did have an infection of the upper respiratory tract at the time he came to the hospital, but that is the only one I can say anything about. I have no good theory as to how the vaccine acts. I think Dr. Karelitz is more able to explain that than I am. As to the leukocytosis that Dr. Bradford asked about, many of the children who were admitted in the acute phase showed it, but practically always a polymorphonuclear leukocytosis rather than lymphocytosis was seen.

The figures of incidence as to sex had struck me, but I felt the series was too small for that factor to have much statistical significance. As to the question on the history of antecedent damage, if all children are given pertussis vaccine, how can we tell whether or not they have had antecedent damage, as Dr. Shaw suggested? Because of the time factor I left out one point. Among this group of 13 children who had convulsions were 2 families in which other members had had febrile convulsions. None of those children who had febrile convulsions showed the kind of neurologic and psychologic changes that the children on whom I reported showed.

I do not know exactly how Dr. Dodd defines febrile convulsions as distinct from encephalopathy. I suppose the convulsions of the 2 children who recovered would be considered febrile convulsions, and the others not. I know of no other means of differentiation.

I am not putting forward this collection of cases as a definite indication that no one should use pertussis vaccine. I think each of us uses smallpox vaccination. We know the vaccine is effective. We do not hesitate to use it. Dr. Moll and I indicated that the question of whether pertussis vaccine can be improved so that these tragedies no longer occur is certainly an open one. My opinion as to whether the risk ought to be taken or not is probably in favor of taking the risk, but I tell the mothers a little about the dangers.

Epidemiology of St. Louis Encephalitis. DR. RUSSELL J. BLATTNER, DR. FLORENCE M. HEYS (by invitation), and DR. MARGARET G. SMITH (by invitation), St. Louis, and DR. ALBERT MILLER (by invitation), New Orleans.

Field and laboratory studies have suggested that the epidemiology of St. Louis encephalitis is a complicated one involving at least two arthropod vectors. Proved interepidemic cases indicate that an endemic focus of this disease exists in the St. Louis area. In 1 such case the virus of St. Louis encephalitis was isolated from the blood of an 8 year old boy who became ill with symptoms and signs of encephalitis and recovered.

Under laboratory conditions the arachnid vector, Dermacentor variabilis, was shown to be capable of becoming infected with the virus of St. Louis encephalitis from feeding on inoculated animals and of transmitting the virus to normal susceptible animals by bite. A female tick, once infected, is able to pass the infection to her offspring. According to our results, the infection persists through all stages of metamorphosis of the second generation into the third generation. Ticks infected under laboratory conditions and kept inactive at a temperature of 12.5 C. (54.5 F.) remained infected for a minimum period of ten months. Eggs laid by an infected female tick and stored in a refrigerator for ten months retained infective virus, and larvae hatched from such eggs at the end of the ten months' storage period likewise were shown to harbor active virus. The virus of St. Louis encephalitis has been shown to occur naturally in the body of the chicken mite (Dermanyssus avium et gallinae), another arachnid collected in this area during nonepidemic

periods. Normal chicken mites raised in the laboratory may be infected readily with the virus by allowing them to feed on chickens with experimentally induced viremia. The mite has been shown to be a potential reservoir for the perpetuation of the virus, since once infected a female mite passes the virus by congenital transfer through the egg and all subsequent stages of development. Culicine mosquitoes are capable of being infected with the virus of St. Louis encephalitis by feeding on chickens with induced viremia. Normal chickens fed on by infected mites showed a viremia for twenty-four to seventy-two hours after the feeding. Uninfected mosquitoes allowed to feed on such chickens acquired the virus, were capable of transmitting it to other (normal) chickens by bite and, to date, have been shown to produce viremia in the hamster by bite. Normal chickens in which viremia was induced by the bite of infected mosquitoes were used to establish colonies of infected chicken mites. Viremia was demonstrated by means of chorioallantoic passage and subsequent inoculation of white Swiss mice, since virus present in the blood was insufficient in quantity to produce encephalitis in mice directly.

These findings appear to indicate that the virus of St. Louis encephalitis might be maintained in nature in chicken mites which are capable of producing viremia in chickens by bite. Under favorable conditions mosquitoes can acquire the virus by feeding on such chickens and might be responsible for carrying the infection to human beings.

DISCUSSION

Dr. Horace L. Hodes, Baltimore: On the subject of mosquito transmission, I should like to ask Dr. Blattner first whether chicken droppings have ever been subjected to the same search for virus that was carried out with blood. The importance of this search, I think, is the possibility that mosquitoes may become infected by feeding on dilute suspensions of other neurotropic viruses.

The second thing of interest is the unusual ability of a mosquito to infect an animal with the small amount of virus which it injects on biting, whereas blood taken from the infected animal is unable to infect the animal even when it is put into the brain.

It seems that one of two explanations is possible. The first possibility is that the virus actually multiplies in the mosquito or in the mite, but this is difficult to show. The other possibility, the one that appeals to me, is that there may be some inhibitor substances in the blood stream of the animal which the mosquito is able to do away with.

Dr. Russell J. Blattner, St. Louis: We have not subjected the chicken droppings to this test, but we feel little doubt that the virus multiplies and is capable of perpetuating itself in some manner in the bodies of chicken mites. Experimentally infected and naturally infected colonies have been maintained in the laboratory for almost three years. Virus is still present in detectable amounts in these mites, and certainly the original ancestors have disappeared long since.

We have not attempted to ascertain whether the larvae of mosquitoes can acquire the virus by feeding on infected material, as was shown in Japanese B. encephalitis. We do know that if one allows a mosquito to feed on heavy suspensions of virus large quantities are taken up, and we have demonstrated that ingested virus remains in the body of the mosquito for at least thirty-two days. After that time it seems to disappear.

The question of multiplication of the virus in the body of the mosquito is unsettled. We have no evidence that it multiples significantly.

Uptake of Radioactive Iodine by the Normal and by the Disordered Thyroid Gland in Children. Dr. Edith H. Quimby and Dr. Donovan J. McCune, New York.

The administration to infants and children by the oral route of carrier-free radioactive iodine in doses of from 20 to 40 microcuries is followed by concentration and retention within the thyroid gland of amounts which vary from about 12 per cent in those without evident thyroid disorder, upward to several fold this value in those with hyperthyroidism and downward to less than 1 per cent in those who show typical hypothyroidism. Values considerably below the mean, and occasionally as low as those in unmistakable hypothyroidism, are observed not only in persons who are only dubiously hypothyroid but also in those whose thyroid function is beyond clinical suspicion of insufficiency. Contrariwise, the values in toxic diffuse goiter (Graves' disease) are not always distinctly above those observed for normal subjects. These limitations to interpretation doubtless depend in part on the fact that hyperthyroidism and hypothyroidism are relative states and show variability in degree. However, nonnumerical examination of the data suggests that sharper results could be obtained by more careful standardization of the test with respect to, among other things, the patient's previous intake of iodine and the state of his health at the time of the observation.

DISCUSSION

Dr. Allan M. Butler, Boston: Did you try the therapeutic effect of administration of thyroid in case 4, or in some of the other similar cases, to see what happened?

Dr. Lawson Wilkins, Baltimore: I should like to ask about the observations on patients who had been receiving thyroid previously.

Dr. Charles Dent (University College), London, England: I should like to suggest that a modification of the new technic for analysis of amino acids that I presented on May 12, 1947, before the Society for Pediatric Research can be used to study the uptake of radioactive iodine in biopsy specimens of the thyroid gland. Using rats, Dr. Fink and I obtained a biopsy specimen, hydrolyzed it and ran it on filter paper. The filter paper was then pressed against a roentgenographic plate, and the location of the radioactive iodine was obtained.

Dr. Donovan J. McCune, New York: In answer to Dr. Butler's question, we have not tested the therapeutic effect of thyroid.

In response to Dr. Wilkins, the administration of thyroid to persons with cretinism has no effect on the uptake of radioactive iodine.

As to Dr. Dent's remarks, we have made a few autoroentgenograms by the usual photographic technic in order to locate the site of radioactive iodine within the gland. I had not heard of the ingenious method that he suggests. We will certainly try it.

Effect of Methyltestosterone on Retention of Calcium and Nitrogen in Growing Boys. Dr. Joseph A. Johnston, Detroit.

In studies of the metabolic changes at puberty, observation was made several years ago of a pronounced fall in the retention of nitrogen and calcium at about the time of the menarche in girls. Further studies were then undertaken to throw light on the specific hormones involved. In the case of girls, at about the age of puberty it was shown that the administration of estrogens resulted in a diminished retention of both nitrogen and calcium. The present study records the effect of the administration of methyltestosterone U. S. P. to growing boys. Definite

increases were observed in the storage of nitrogen, but consistent depressions occurred in the calcium balances which were comparable to those noted when estrogens were administered to girls.

DISCUSSION

DR. LAWSON WILKINS, Baltimore: I should like to ask whether in these boys epiphysial fusions had taken place, or were the patients still growing?

DR. JOSEPH A. JOHNSTON, Detroit: The children were all still growing. The oldest boy was 14 years of age.

DR. ALLAN M. BUTLER, Boston: How long was methyltestosterone administered?

DR. JOSEPH A. JOHNSTON, Detroit: It was given every other day for eighteen days, except in 1 case, in which it was given every other day for thirty-six days.

DR. ALLAN M. BUTLER, Boston: When did the balance study start in relation to the beginning of the methyltestosterone therapy?

DR. JOSEPH A. JOHNSTON, Detroit: In each case an eighteen day control period preceded the administration of the methyltestosterone, and a third period of eighteen days followed.

Nephrotic Crises. DR. LEE E. FARR, Wilmington, Del.

The biochemical deviations from normal which are known to occur in children with the high clearance type of the nephrotic syndrome can be classified into a very few groups on the basis of the physiologic and metabolic systems involved. This classification is independent, to a considerable extent, of possible primary etiologic factors. Close examination of these data indicates that likely only a few of the observations are made on systems which are primarily disturbed and that the majority of the apparent aberrations from normal are secondary effects of those primary disorders. For a system to be considered the site of a primary disturbance, conclusive evidence must be adduced showing that alteration of this single component or group of components profoundly affects the expected course of the disease. Studies carried out for the past twelve years indicated that the plasma hypoaminoacidemia characteristic of these patients is a reflection of a primary disturbance. The unique biochemical change associated with nephrotic crises is an increase in the hypoaminoacidemia which develops with startling rapidity and is reflected in a characteristic clinical syndrome. These crises are frequently associated with infection of the blood stream and peritoneal cavity, and when such is the case the expected mortality is approximately 60 per cent. Intravenous administration of protein hydrolysates without adjuvent chemotherapy is itself capable of reducing this mortality to zero. Such striking reversal of the expected course can be attributed only to a correction of a fundamental disturbance. In nephrotic children not in crisis, intravenous administration of protein hydrolysates uniformly results in elimination of paradoxic dumping of nitrogen in those with high nitrogen intakes, and occasionally such treatment early in the disease may be followed by prompt and complete recovery. It is reasonable to assume that the hypoalbuminemia and the increased minimal requirements of nitrogen of these children are secondary manifestations of the same primary disorder. The hypothesis is advanced that retention of sodium is a similar measure of a possible second primary disturbance involving the electrolytes and that the high clearances observed in these patients are in a sense a compensatory effort of the kidney to maintain excretion of sodium. Direct evidence for this hypothesis is lacking, but correlation between changes in clearance and clinical condition has been observed. Thus far, no evidence has been obtained which indicates other possible measure-

ments of the primary disturbance. It is hoped that if the controlling mechanism of the disorder can be discovered satisfactory procedures for treatment of the patients can be evolved without knowledge of the causative agents themselves, which presumably act merely as a trigger mechanism.

DISCUSSION

DR. DANIEL C. DARROW, New Haven, Conn.: What do you mean by "paradoxic dumping?"

DR. CHARLES DENT (University College), London, England: Why were the acids so low in the plasma?

DR. LAWSON WILKINS, Baltimore: What about the excretion of amino acids in the urine?

DR. ALLAN M. BUTLER, Boston: Did I understand Dr. Farr to say that the high clearances were associated with an increased flow of blood through the kidney? That is hard for me to believe. Is something wrong with my preconceived ideas or with the methods used in determining the flow of blood?

It is difficult for some of us to feel that the so-called nephrotic crisis is the result of the low amino acids in the blood. If I am not mistaken, low levels of amino acids in the blood occur in other conditions, particularly infections, and no syndrome such as occurs in the so-called crisis of nephrotic patients appears.

It is particularly hard for some of us to think that the symptoms of nephrotic crisis referable to the abdomen are associated with a low amino acid level in the blood. There is considerable evidence that these symptoms may be associated with partial or almost complete intestinal obstruction due to edema of the intestinal wall.

In our experience my colleagues and I are impressed with the difficulty of making a differential diagnosis between early peritonitis and intestinal obstruction due to such edema.

I hope the discussion on this point will be free, because if many of us are missing a specific therapy for crises in our patients with nephrosis, namely, the specific treatment with amino acids, then we are practicing poor medicine; on the other hand, if we resort to amino acid therapy without adequate evidence that it is effective, that also is practicing poor medicine.

DR. MITCHELL I. RUBIN, Buffalo, N. Y.: Regarding the "apparent" absence of infection which Dr. Farr spoke of, I think each of us has seen children with nephrosis in whom physical examination demonstrates no evidence of infection, yet repeated blood culture yields organisms indicating infection of the blood stream. It seems to me that, in the last several years, the best therapy for the control of the crises has been with chemotherapeutic and antibiotic agents. My colleagues and I have had several patients to whom we administered amino acids without the striking benefits obtained from the sulfonamide compounds and penicillin.

The values for renal clearance for our patients with nephrosis showed that the renal plasma flow, the glomerular filtration rate and the tubal excretion were increased. However, the percentage of increase was not always similar in these three functions. The reason for these increased clearance values has not been elucidated.

DR. JOHN D. LYTTLE, Los Angeles: I have never been able to find what comes first in nephrosis. It seems probable that the clinical signs and symptoms, the lipemia, hypoalbuminemia and hypoaminoacidemia are secondary. I first see the patient at the onset of edema when the disease has been going on for some time. I do not see how Dr. Farr can assume that hypoaminoacidemia is the first change, but it is an interesting theory, and the amino acid level may be important since it is the last to return to normal.

Dr. Katharine Dodd, Cincinnati: Disease varies a great deal from place to place. Possibly this variation accounts for the fact that during the three and a half years of my residence in Cincinnati I have seen a great many more patients with nephrosis than I ever had before. During this period my associates and I have nearly always had 3 or 4 such patients in the hospital. Some of the patients died of nephritis. Of those in whom nephritis did not develop only 2 died. It is pertinent to inquire what caused their deaths. One of these patients had a thrombosis of the inferior vena cava, and the thrombus extended into the right hepatic vein, the renal vein and the splenic vein. The terminal illness developed in the other patient while under treatment by his private physician at home. The illness started with vomiting and diarrhea. The physician increased the dose of the sulfonamide compound but did nothing else. When the patient finally entered the hospital, administration of penicillin was started. The culture of the blood yielded pneumococcus. The patient died, and the autopsy revealed a tremendous amount of pneumococcus peritonitis.

All our other patients are doing excellently at present. Some of them are well. Some still have their nephrosis. Treatment involved no more than conventional procedures: paracentesis when indicated; occasional transfusions when anemia developed; maintenance on prophylactic doses of sulfonamide drugs; the use of penicillin whenever there was evidence of possible infection. Certainly, in Cincinnati we are unaware of what has been called a "nephrotic crisis" except as the term applies to difficulties associated with infection. It is difficult for me to believe that anything except infection and the development of chronic nephritis complicates the progress of the disease in our patients.

Dr. Donovan J. McCune, New York: Some of us have been confused by the discrepancy between our limited but unsatisfactory experience of the therapeutic effect of albumin on nephrotic edema and the glowing claims which have been made before this society and lately in the daily press. May I ask any one in the audience who has invesigated the matter to make this point clear?

Dr. Charles A. Janeway, Boston: No one has had a statistically significant experience with the use of albumin. I believe the only patient on whom a report was published that my associates and I had a chance to treat with an amount of albumin sufficient to permit satisfactory results, considered in the light of subsequent experience, presumably had a spontaneous diuresis at the time he was given albumin. Subsequent to that we have had the opportunity to treat a small number of patients. We have seen some of the patients whom Dr. G. W. Thorn, of Boston, has treated. In my experience, of the diuretic agents available for the treatment of nephrosis, albumin with a low salt content is capable of eliciting diuresis more constantly than any other injectable substance. It is not capable of eliciting diuresis every time. The salt content makes a great difference. We had a few patients in whom one definitely could show that a matter of a mere 0.5 Gm. of salt made the difference between diuresis and failure to elicit diuresis.

That the diuresis is due to albumin I think can be proved by the fact that the minute albumin is stopped the curve for weight starts to ascend; the minute administration of albumin is reinstituted, the curve comes down again. We have kept such records for every patient recently to demonstrate that the diuresis is due to albumin, not to some spontaneous change occurring in the patient.

The reason for failures in a few patients I am sure I do not know. We have not been able to detect the difference between these patients and the others.

One also must add that the administration of albumin to these patients is much like pouring something into a sieve. Most of the albumin intake appears in the

urine. The loss of weight which accompanies administration of albumin is gradual. It is usually steady and progressive, unless intercurrent infection occurs to stop the good results. It is entirely different from the type of loss of weight one sees after spontaneous diuresis, such as occurs either after no specific episode or oftenest after an infection of one sort or another. In such patients, if an adequate diuresis occurs, recovery takes place in three or four days, as happened with Dr. McCune's patients after administration of sodium and potassium salts. The loss of weight is 3 or 4 pounds (1,361 to 1,814 Gm.) a day, whereas with albumin loss of weight is on the order of ½ pound (227 Gm.) per day, and it may take thirty or forty days to get a comparable loss in weight.

I can say little more about albumin because I do not think adequate data are available at the moment. It provides a way, in a great many patients, of eliciting diuresis if it cannot be done by some other means; the treatment probably requires large doses kept up for nearly a month to eliminate all the edema fluid, and in those patients for whom smaller amounts have been used so far there is a tendency for the edema to recur. This therapy is much like administering iodine to a hyperthyroid patient; all one does is suppress the symptoms temporarily, while the natural course of the disease is run underneath.

I should like to substantiate some of the other things said here. I cannot talk about nephrotic crises and the use of amino acids with any confidence because I have not used them, but it would seem that most crises are associated with infection. I am not sure, however, that the infections do not develop after the progress of the disease begins to allow edema to accumulate. I have 1 patient who has been under extremely close observation by her father, who is a physician, and his observations certainly suggest that the first thing which occurs is the accumulation of edema, then, secondarily, the infections appear, and finally the symptoms which are called crises are likely to occur. Certainly, these crises are short lived with our modern methods of chemotherapy. Perhaps we have been negligent in not using amino acids more than we have.

DR. A. ASHLEY WEECH, Cincinnati: One thing needs to be stressed in the management of nephrosis and that is what it means to parents to have a nephrotic child. Month after month and year after year they endure distress and worry. They wonder whether they have the right physician or should change to another. In these circumstances the kindest thing one can do is to keep the ratio between days in the hospital and days at home as low as possible. I myself have been guilty of outbursts of therapeutic enthusiasm during which patients have been kept in the hospital for weeks and weeks while one method of treatment after another was tried. Some of the procedures have occasionally been effective in provoking diuresis, but all methods have been without avail in altering the course of the disorder. We are now trying a different procedure. The patients are kept at home on prophylactic sulfonamide therapy. In the severest stage of the disease they are brought into the hospital about once a month for paracentesis and perhaps a blood transfusion. Both procedures can be carried out within twenty-four hours and the patient sent home. Our results are just as satisfactory as they ever were.

DR. ALLAN M. BUTLER, Boston: Dr. Weech suggested the desirability of giving these patients prophylactic sulfonamide therapy. Our experience in using sulfonamide compounds to control streptococcic and pneumococcic infections before we had penicillin impressed us with the undesirability of using sulfonamide drugs in patients with nephrosis. Is there reason, Dr. Weech, for us to change our opinion?

DR. A. ASHLEY WEECH, Cincinnati: Examination of the records of patients for a number of years shows that the majority of those who die succumb to pneumococcic infection. Life can be saved if these infections can be prevented. A fear

has been expressed that sulfonamide drugs given to a patient with existing renal injury might enhance the damage. The danger cannot be very great. Prophylactic doses are small, not over 2 Gm. a day even for a large child, and for most children with nephrosis about 1 Gm. a day is sufficient. Most of our patients have been on this routine during the past two years. We have had no difficulty from it.

Dr. Joseph A. Johnston, Detroit: My associates and I have routinely used one of the sulfonamide drugs as a prophylactic agent for a number of years. During that time we followed 14 patients, but of these the condition of only 8 can be thought of as pure nephrosis without any evidence of glomerular involvement. Of these, 6 patients have made complete recoveries. The time required averaged a little over two years. Two still show signs of slight nephrotic activity as judged by albuminuria. None has died of intercurrent infection, and the first patient with peritonitis that we encountered after the sulfonamide drugs were introduced was practically anemic after this was used. Her pneumococcic peritonitis cleared in twenty-eight hours.

I agree, Dr. Weech, with your idea of managing these children with a minimum of inpatient care. We commonly handle these patients as outpatients; the most successfully managed one required paracenteses and transfusions from time to time, both of which were done during outpatient visits.

Dr. Lee E. Farr, Wilmington, Del.: In answer to Dr. Darrow's question concerning paradoxic dumping, the term was first used, I believe, by Dr. J. L. Gamble, of Boston, in a study on some normal infants in which he observed that as he increased the dietary nitrogen beyond what is now considered to be the optimal intake the increase in urinary nitrogen became greater than the increase in dietary nitrogen. He termed this phenomenon paradoxic dumping.

In answer to the question as to the qualitative study of the amino acids, unfortunately, my associates and I did not know the chromatographic method. We have no specific information on that point. I can say that analysis of the blood plasma by the Van Slyke nitrous acid method and the ninhydrin aminonitrogen technic shows a changing ratio during crises which indicates qualitative, as well as quantitative, change. The amino acid nitrogen in the urine is within the normal range in these patients.

As to the question regarding increased flow of renal blood, I can say that using the methods for the elucidation of renal physiologic mechanisms which were devised in numerous clinics, including that of Dr. Homer Smith, of New York, and others, we obtained data which indicate an increase in renal blood flow which is enormous. In some of these patients the apparent minute renal blood flow would be approximately 15 to 20 per cent of the presumed blood volume, which is certainly a large figure.

It is true that in infections, such as chronic osteomyelitis, pneumonia and tuberculosis, the plasma amino acids are below the normal level to some extent. However, I remind you that I said specifically the hypoaminoacidemia in nephrosis was not the primary disturbance but a measure of the primary disturbance. I believe that the mechanism which results in decreased plasma amino acids in the nephrotic patient is different from the mechanism resulting in the decrease in plasma amino acids seen in infectious conditions, or the decrease which can be produced in normal persons at will by the administration of anesthetic agents, by surgical procedures, or merely by the inhalation of gas which is low in oxygen content.

In each of these instances the disturbance is limited, for the most part, to the duration of the exciting cause. Those instances show no evidence of any significant, severe, or profound alterations in protein metabolism of the nature seen in nephrosis.

Dr. Butler asked about the association of abdominal pain with a low level of amino acids in the blood. I do not think this condition is the cause of pain, but in nephrotic patients the presenting clinical symptoms of a crisis are abdominal pain and fever. The definitive diagnosis of nephrotic crisis can be made only by analysis of the blood. Therefore, the development of sudden unexplained abdominal pain with fever in nephrotic children has become for us a criterion requiring analysis of the plasma amino acids to help us determine whether we are dealing with an intestinal disturbance, perhaps obstruction, perhaps infection, or with the early phases of a nephrotic crisis. Treatment is immediately instituted without waiting for the laboratory report.

Dr. Lyttle brought up the question as to whether or not hypoaminoacidemia preceded the clinical disease. I do not know. I can say it is the last manifestation to disappear. It may be the first thing to appear, but we have no way of assaying our general population to determine the incidence of hypoaminoacidemia in them.

The severity of hypoaminoacidemia in nephrotic crises is far beyond that which is seen in other conditions. I have never seen the plasma amino acid nitrogen level below 2.5 mg. per hundred cubic centimeters in patients other than those in nephrotic crises as measured by the ninhydrin technic. Patients with pneumococcic pneumonia come the closest to it. We have seen their levels as low as 2.75 mg., but a nephrotic crisis does not develop until the amino acid level has fallen below 2.5 mg. This value is a statistical average. There is some slight variation among persons, but it does not appear to be much greater than 0.1 to 0.2 mg. per hundred cubic centimeters.

Dr. Dodd brought up the question of nephritis. The group of patients which I discussed today were those with high clearances and I advisedly and designedly left out of the discussion that group of patients exhibiting usual manifestations of the nephrotic syndrome who had a urea clearance of 100 per cent or less. In the nephrotic patient with high clearance the disease may persist for as long as sixteen years without diminution of the clearance below 120 per cent of normal and without significant improvement in hypoproteinemia. Such a course is certainly different from that seen in usual hemorrhagic nephritis. I believe the disease is different, and some of the phenomena we have discussed this morning substantiate this belief, as I have never seen crises in hemorrhagic nephritis. The pros and cons are too long to go into at this time, but I wish to point out that the disease syndrome I have discussed begins only in young children, with a peak incidence at just under 4 years of age. It does not begin in adults. This incidence is strikingly different from that of hemorrhagic nephritis. Patients with high clearance nephrotic syndrome can die of renal failure and cardiac failure, but Dr. J. E. Smadel, of Washington, D. C., and myself think that the mechanism of renal failure in these patients is different from that generally presumed to operate in chronic glomerular nephritis.

As to crises in Cincinnati and the fact that they have not been seen there, have they been looked for, and have you analyzed the blood of your patients for amino acids? There is no other way that I know of to make a certain clinical diagnosis. This is one of the instances in which we have to rely on the laboratory for confirmation of our clinical impression.

We have no highly effective specific treatment for nephrosis, unfortunately. The administration of amino acids is not a specific therapy for the syndrome. It is a means of carrying patients through numerous critical episodes which in the past have been associated with a high mortality. Whether eventually it will be possible by such means to cure the patient of the disease, the future will tell.

The administration of sulfonamide drugs or penicillin prophylactically, I think, should be at the discretion of the physician. If the patient is subject to repeated infections, there is probably no great harm done by such a procedure.

As far as keeping these patients in the hospital is concerned, a few of us have to keep them in to try to find out what is going on, but I believe as a general rule these patients are kept in the hospital too long and too little is done for them. By and large, they will do almost as well at home, if cooperative parents will bring the patients into the hospital whenever there are signs of impending difficulty.

Disturbances in Body Water and Electrolyte in Dehydration of Diarrhea.

DR. DANIEL C. DARROW, DR. JAMES FLETT JR. and DR. EDWARD L. PRATT, New Haven, Conn.

These studies represent a detailed investigation on the electrolyte and water balance during recovery in 6 cases of diarrhea. The studies confirm previous observations that the deficit of electrolyte involves loss of sodium, chloride and potassium. Treatment without potassium leads to the transfer of large amounts of sodium to the cells and potassium is retained only when food is taken. Some transfer of sodium to the cells may occur in the initial phase when potassium is used, but at the same time potassium also is retained. The data show that in the treatment of acidosis as much as 60 per cent of the sodium given as sodium bicarbonate may enter the cells. On the other hand, only a small amount of sodium may enter the cells. Hence, the calculation of the rise in serum bicarbonate to be anticipated from a given dose of sodium bicarbonate is at present unpredictable. In some cases sufficient sodium is retained to raise serum bicarbonate to normal levels theoretically, but so much sodium enters the cells that serum bicarbonate remains low.

The data show that imperceptible loss of water is sometimes so high that sweat must be four to five times as great as the imperceptible loss of water, which is presumably related to caloric production. The electrolyte loss in sweat must be considerable, and allowance for loss of sodium and chloride in sweat must be made in order to make the apparent retentions of sodium and chloride reasonable.

One patient showed retention of cellular phosphate during recovery. This retention has not been demonstrated in the other studies, but deficit of potassium has been found in the muscle of babies dying of diarrhea.

DISCUSSION

DR. SAMUEL RAPOPORT, Cincinnati: Dr. Darrow has stressed the great losses in the form of sweat that these babies suffer, and I should like to point out that this conclusion is hypothetic in nature, since he did not measure those losses of sweat. He based his calculations on the changes in total weight and water balance and on losses through the lungs, which he assumed to be in a direct relation to the caloric expenditure. As you realize, during a period of extreme loss of weight the loss of water vapor will no longer bear such a relation and to that extent his conclusion is doubtful; furthermore, from a clinical view, the statement or the impression that sweat is such an important factor is difficult for me to accept.

Actually, the typical clinical description given by the older clinicians is that of a dry baby: the skin has ceased to excrete sweat. As a case in point, my associates and I tried to find out whether an infant with diarrhea—the one on whom we presented data yesterday—actually did sweat. We put starch, iodine and other such materials on its skin, and there was not a trace of sweat.

During the period of extreme loss of weight in this baby, the loss of water, which must have been through the lungs, the insensible water loss, was at the rate of ten times that of normal babies, and I wonder to what extent all this has a bearing on Dr. Darrow's statement. One implication of his stress on sweat is that the sodium and chloride intakes must be higher than those recommended by either Dr. Butler or ourselves. Since obviously in the sweat sodium and chloride are present even though in variable amounts—he stated 20 to 80 milliequivalents per liter—I think less sodium and chloride would be sufficient.

I am pleased that he stressed the great intakes of water without electrolytes which are necessary. Whether the water is lost partly through the skin or entirely through the lungs, he recommends the administration of 5 or 10 per cent glucose solution. However, in small babies we have had an unfortunate experience with 10 per cent glucose solution given at rates of about 40 cc. per hour. The babies lost electrolytes in the urine with the glycosuria. Five per cent glucose solution did not have this effect.

I should like to comment on the first experiment that Dr. Darrow presented, that on the baby in whom diarrhea developed and who was fed added potassium. I think it brings up a point which should be stressed, that is, the difference between the dehydration phase and the postdehydration phase. Methods of treatment which are appropriate after the recovery phase are inappropriate before. In this baby, according to Dr. Darrow's statement, a serum potassium level of 9.6 millimols per kilogram of body weight developed. This level has been reported in the fatal potassium intoxications and is one which may occasionally lead to heart block. The emphasis then should be that such treatment is necessary only after hydration of the infants in the postdehydration phase and that the therapy is not prophylactic.

DR. ALLAN M. BUTLER, Boston: I thought Dr. Darrow said, as he told of the baby's going into a state of dehydration, that it lost 6.3 milliequivalents of sodium per kilogram. Shortly thereafter he said that in replacement therapy the baby needed 12 milliequivalents of sodium per kilogram.

DR. D. C. DARROW, New Haven, Conn.: The figure was 12 millimols per kilogram.

DR. ALLAN M. BUTLER, Boston: Intracellular repair required 5 milliequivalents per kilogram, which, with the aforementioned figure, totals 17. I could not make the arithmetic balance, as I had a loss of 6.3 milliequivalents against the 17 milliequivalents recommended for repair.

DR. D. C. DARROW, New Haven, Conn.: Seventeen is a maximal, theoretic figure.

DR. ALLAN M. BUTLER, Boston: One of the reasons for getting the arithmetic straight is that many of our babies are drowned with sodium from the administration of huge amounts of sodium bicarbonate. This results from theoretically false calculations as to bicarbonate loss, together with administration of large amounts of isotonic solution of sodium chloride. If one looks up the literature, one will find that in repairing dehydrated babies many authors recommend giving 20 milliequivalents of sodium per kilogram in the course of their reparative therapy, when 6.3 milliequivalents is perhaps the loss that is being replaced. I do not need to emphasize the seriousness of overtherapy. In reading a recent paper by Dr. Rapoport, in which he described a syndrome due to hypocalcemia in the course of rehydration of dehydrated babies, I wondered whether the syndrome is not the result of excessive electrolyte therapy.

DR. D. C. DARROW, New Haven, Conn.: I realize the dangers of making the assumptions we did in ascribing all the increase in imperceptible loss of water to sweat, and I recognize that a great deal of the increase may be accounted for by increased losses from the lungs. However, the conclusion that sweat accounted for a large proportion of the increase in "imperceptible loss of water" is based on measurements of large electrolyte retentions that cannot possibly be reconciled with our knowledge of the normal contents of body fluid, and one can be sure there must have been false retentions in our data. The only way we can reconcile our apparent retentions is by assuming that sweat occurs.

Now, certain of the babies that showed this phenomenon had obvious sweat on their skin, and one did not have to use iodine paper to see the sweat—it was there in droplets and soaked the linen.

On the other hand, you must remember that these measurements were made on babies that were being treated, not on the babies as they came into the hospital. Observations were started from the extreme dehydration point and continued as the babies recovered; the exception was the baby I showed you, in whom the dehydration developed under our eyes, so to speak, as an experiment. The high concentration of potassium in the serum of this child must not be regarded as a result of our usual therapy for diarrhea, for this baby was subjected to an experiment during which dehydration developed. As a matter of fact, I do not think I have ever seen—I do not think the data in the literature show—the appearance of heart block until the concentration of potassium reaches at least 10 millimols per liter. However, a dangerously high level of serum potassium undoubtedly developed in this baby.

I am sorry that I created confusion with my statement in the summary. When I spoke of the amounts of electrolyte retained during recovery, I referred to the amounts that I can show were retained in the various cases. The figures represent maximum apparent deficits in these babies, and my calculations from the composition of the bodies of those who died fit in with these data. If specific cases are discussed, figures would be somewhat lower; but I can show you certain cases in which these levels will be reached. In the infant that we are speaking of the full-fledged picture did not develop. I think it would have taken another day before he reached what could be called extreme dehydration. The experiment was stopped in two days. We did not want it to go on any longer, so I do not think reconciliation of the actual data from that case with results in the others should be attempted.

I think that any one's data on balances will show a certain amount of wastage of sodium and chloride in the stools and urine, so that the figure I gave you for treatment, while it is an amount over and above that actually retained, is justified by the fact that one cannot hit the amounts retained exactly on the mark, and I doubt that the urine and kidneys would let you obtain the correct balance if you tried to hit it exactly on the mark. You would find the kidneys were wasting electrolyte and you were undertreating the babies.

I agree with Dr. Butler that the dangers of giving too much sodium and chloride are great, and particularly excessive amounts of sodium bicarbonate. Since we have followed a little more systematic method of treating these infants, I think we practically never see the edema that used to develop when we merely gave them sodium and chloride and did not pay too much attention to the amount of sodium chloride in relation to the total water given.

I am sure Dr. Butler, Dr. Rapoport and I agree as to the approximate amounts of solution we give. What I am pleading for, particularly in instances that you have not been conscious of these problems, is that you do not give glucose in

isotonic solution of sodium chloride in the mistaken notion that you are getting the chief benefit from the use of glucose solutions, which is the administration of water without salt.

Persistent Infectious Diarrhea of Infants. Dr. Gertrud C. Reyersbach, Dr. Allan M. Butler and Dr. Nathan B. Talbot, Boston.

We wish to summarize our clinical observations on a group of 40 infants with protracted nonbacterial infectious diarrhea who were treated at the Children's Medical Service of the Massachusetts General Hospital. Our purpose in presenting these clinical observations is to stimulate an exchange of opinion among members of this society with the hope that it may assist all of us in coping with one of the most serious diseases of infancy. The information presented in the charts and tables pertains to 35 infants who were treated last year, all but 1 of whom recovered. Five babies treated this year will be discussed separately. There were no fatalities in this group.

My first chart depicts the place the infection was contracted. Of the 35 infants covered in this chart 15 contracted the infection in other hospitals, the majority of these in units for the newborn. Four contracted the infection at home. Sixteen contracted the disease by cross infection from infants admitted to our service with this type of diarrhea. Most of the cross infection occurred before the specific type of this disease and its readiness to spread had been appreciated. The majority of the infants were under 1 year of age, but infants as old as 13 months of age had severe illness from this infection. The age limit described in the chart in itself emphasizes the fact that the disease did not occur in recognizable form in older infants or children.

Chart 2 describes the number of days of diarrhea these patients had when oral feedings were not given for at least twenty-four hours, diarrhea being defined as more than three liquid stools a day. Twenty of the babies had diarrhea for more than three days when not receiving oral feedings. One infant had thirty-two days of such diarrhea.

Chart 3 describes both the number of days these patients were hospitalized and the number of days they received fluids intravenously. The fluids consisted of 150 to 200 cc. per kilogram of body weight per day of the 10 per cent glucose solution containing potassium, sodium chloride and phosphate (30 milliequivalents of sodium, 22 milliequivalents of chloride, 20 milliequivalents of lactate, 15 milliequivalents of potassium and 3 milliequivalents of hydrogen phosphate per liter) as described in the paper read before this society last year (Butler, A. M., and others: Parenteral Fluid Therapy in Diarrheal Disease, *Am. J. Dis. Child.* **72**:481 [Oct.] 1946) together with 50 to 100 cc. of isotonic sodium chloride solution per day and frequent transfusions of plasma and whole blood. The desirability of the hypotonicity of our repair solution in sodium and chloride was emphasized last year. It can be seen that all patients remained in the hospital for ten days and that all patients received fluid intravenously for at least six days. Fifty per cent of the patients remained in the hospital for thirty days, and 50 per cent received fluids intravenously for twenty days. One of the patients remained in the hospital for seventy-two days and received fluids for sixty days.

A wide range of certain blood and serum concentrations was observed on admission, the concentrations in most instances being unpredictable from the history and the results of the physical examination on admission.

There were a number of complications. Most of them resulted from bacterial infection. Deserving special comment is the circulatory collapse that occurred

in 4 of the patients during therapy. The transient congestive failure that occurred in 1 patient after the inadvertent administration of 30 cc. of whole blood per kilogram of body weight also merits special emphasis.

A variety of therapeutic methods were used other than those pertaining strictly to nutrition. All of the patients in the group under treatment received at least 1 transfusion—one baby had 19—and that there was an average of 4.6 transfusions per baby. Though sulfadiazine and penicillin were given to a large number of babies, we were not impressed with the efficacy of such therapy unless the infant had an infection for which the drugs were specific. Twenty-six babies received infusions of plasma. One baby received 14 such infusions, the average per baby being 5.3. Since plasma provided no apparent benefit not provided by transfusions of whole blood and since pooled plasma carries a greater risk of transmitting infectious hepatitis than blood, plasma should be used with caution. Camphorated opium tincture U.S.P. and adrenal cortex extract resulted in no apparent benefit. The combination of desoxycorticosterone acetate and fluids administered intravenously frequently resulted in edema, first detectable in the buccal mucous membranes. The use of desoxycorticosterone acetate with intravenous administration of isotonic sodium chloride solution for a patient depleted of potassium may well cause a disturbance in the electrolyte concentration of tissue that might be deleterious. Hence, this therapy should be undertaken only with the greatest caution. From theoretic considerations we are inclined to believe that desoxycorticosterone acetate should be used only with great precaution, as it may involve a risk out of proportion to the possible benefit.

Different types of foodstuffs were used when oral feeding was started after periods of intravenous nutrition. No one type of food seemed more successful than others, the success of all foods apparently depending more on the stage of the disease than on the type of food.

Repeated examination of the stools of the babies treated last year and of those treated this year revealed no occult blood. Of the 10 determinations of serum calcium made at random in the course of therapy, none revealed a concentration of less than 8.5 mg. per hundred cubic centimeters. Nor have we observed the symptoms described by Rapoport and associates in the postacidotic state. Indeed, one wonders if those symptoms are not dependent on excessive rehydration therapy with sodium and chloride.

After initial hydration, the intravenous infusions of the 10 per cent solution of glucose and electrolytes did not result in hyperglycemia detectable on analyses of urine and blood for sugar. The one mortality among these 40 patients was that of a 4 month old infant who had had difficulty in breathing from birth, with a tendency to assume a position of opisthotonos and to display athetoid movements. Death occurred after an acute episode of respiratory distress and cyanosis. No anatomic cause of death was observed. Cultures of the blood yielded no pathogens. There was no pathologic change in the gastrointestinal tract.

In treating the 5 babies cared for this year, we studied the effectivenes of giving orally the previously described 10 per cent solution of glucose and electrolyte after initial parenteral rehydration was accomplished. Whole blood transfusions were provided as indicated. From 160 to 200 cc. of glucose and electrolyte solution per kilogram per day was given orally. Comparison of these babies with those treated last year with frequent parenteral therapy showed the following differences:

1. The oral feedings tended to provide less caloric value. This deficit was perhaps increased by loss in the augmented stools.

2. Less adequate hydration was reflected in higher concentrations of hemoglobin and serum protein throughout the course of therapy.

3. The babies had on the average a greater number of stools.

4. These three factors pertaining to the oral feeding resulted in a slightly greater loss of weight during therapy.

5. It was felt that the babies receiving the oral therapy were quieter and happier than those receiving the intravenous therapy.

It is our impression that such oral therapy may be beneficial when parenteral therapy is imposible. However, initial hydration with parenteral therapy is desirable. Thereafter, such oral therapy alone or in conjunction with parenteral therapy may be tried.

DISCUSSION

Dr. George M. Guest, Cincinnati: Since Dr. Butler has implied that the postacidotic syndrome, with hypocalcemia, recently described by Dr. Rapoport, Dr. Dodd and their co-workers, resulted from the type of therapy employed (correction of acidosis with sodium bicarbonate solution), I should like to suggest that he may have misinterpreted the chief point in their report. Some of the background of this thesis was furnished by studies on the depletion of intracellular potassium and organic acid-soluble phosphates in diabetic acidosis, which Dr. Rapoport and I presented at several past meetings, and by studies, such as those of Atchley and associates, on mineral balances in diabetic acidosis. With the development of acidosis, due either to diabetes or to gastroenteritis, liberation of phosphate and potassium and other intracellular components of blood and tissue cells leads to increased urinary excretion of those elements, if renal function is unimpaired, and consequent depletion of the stores of those elements in the body. Dr. Butler at our meeting last year discussed the importance of "demineralization" in acidosis, involving losses of sodium, potassium and phosphate, and he included potassium and phosphate in fluids he employed for replacement therapy, supplying the elements needed mainly for resynthesis of intracellular constituents. With recovery from acidosis the concentrations of potassium and phosphate in the plasma may fall to extremely low values when rapid resynthesis of intracellular organic constituents depletes the supply of those elements in the extracellular fluid. The occurrence of hypocalcemia in the postacidotic period is similarly explained by rapid replacement of calcium in the tissues (i. e., bones) from the available supply in the extracellular fluid. A lowered concentration of serum calcium after the administration of alkali may be accepted as positive evidence of antecedent depletion, rather than an effect of the alkali per se. A moderate degree of alkalosis brought about by administration of alkali to a normal subject does not lead to hypocalcemia. It should be mentioned that mild alkalosis may be observed in the period of recovery from diabetic coma in cases in which neither sodium bicarbonate nor sodium lactate has been administered for initial correction of the acidosis. A mild state of alkalosis in the postacidotic period might depress the ionization of calcium but not the concentration. Hypocalcemia, together with low values for serum potassium and phosphorus, in the postacidotic period indicates a need for more complete replacement therapy than has been practiced in the past. The fact that correction of acidosis with alkali favors and accentuates the rapid uptake of these elements in the tissues is an argument for such therapy.

Dr. Edward L. Pratt, New Haven, Conn.: For the last year I have devoted most of my time to the study of diarrhea. What I discovered in a year, you have found out in a few days—that is, that the subject is extremely complex.

Our own studies, which were reported by Dr. Darrow and Dr. Flett, you know. I think Dr. Butler is right in feeling that the important workers were the members of the house staff who carried out these long programs of intravenous therapy,

which, as he showed, are possible in his institution and in a few others in the country. However, in traveling about, I was impressed with the fact that few persons could carry out such an extensive program, particularly those who have many other patients to take care of in the course of one day, so that it is encouraging to see that oral therapy is not like the Kenny therapy, which works for only one or two persons, but that others can apply it with good results.

In our own studies we have not seen low serum calcium levels apparently present, either on a clinical basis or on measurements taken when we thought the level might be reduced. Potassium intoxication has not been observed in our own subjects except in the patient reported on previously by Dr. C. D. Govan Jr. and Dr. W. W. Weiseth. Several patients I think we undertreated with potassium because we were afraid that potassium intoxication was the cause of their trouble. We were fortunate to get measurements which showed conclusively that the important factor was not potassium intoxication but was more likely a deficit of potassium in the cells.

The question of phosphorus is even more baffling to us after studying it than it was before. We have not been able to show any great deficit in phosphorus so far as the retentions that occur when the patients recover to an apparently normal state are concerned; however, patients who have died usually do show low levels of phosphorus in the cells. Perhaps we cannot observe the patients long enough to show this shift in phosphorus. The only patient who had a really significant deficit of phosphorus was 1 treated for the first two periods entirely with sodium and chloride without potassium. All these patients show a fairly high concentration of phosphorus in the urine, but they show astonishingly great retention of phosphorus whenever calcium balances are positive.

I believe that none of us has the solution to feeding babies with diarrhea, but I think Dr. Butler and Dr. Weech have the correct approach: observation of the patient. This is very important, but I think there are many myths in the treatment of diarrhea, and Dr. A. W. Chung's quantitative studies are to be commended. In studying diarrhea we should try to substitute, wherever possible, quantitative data for clinical observation.

Dr. Charles Hendee Smith, New York: I should like to ask Dr. Butler two questions. Has he any idea of the mode of transmission of infectious diarrhea on his service? It is an unfortunate and remarkable thing that children who come into a hospital for one disease go out—and often through the back door—with another disease. In studying this problem years ago at Bellevue Hospital, my colleagues and I decided that the commonest source of transmission of intestinal disorders was through the nipple technic.

I do not know the technic in all your hospitals, but I do know what it is in many hospitals, that is, the nurse who changes the diaper puts the nipple on the bottle. I have been called in on a number of epidemics of diarrhea of the newborn, and in no instance did that condition fail to obtain. The bottles come to the nursery with a sterile cap or cork. The nipples come in glass jars, sterilized. The nurse changes the diaper, gives her hands a cursory wash and puts the nipple on. In a number of hospitals that technic was stopped, and the nipples were put on in the diet kitchen, or they were put on by a nurse who had not that day changed a baby. In these hospitals the sporadic outbreaks of diarrhea ceased. At Bellevue the nipples were put on by a nurse who scrubbed her hands surgically and then put on rubber gloves.

In another hospital with intermittent diarrhea in the nursery for the newborn, not a major epidemic of diarrhea, but a good deal too much of it, the outbreaks were stopped simply by putting a sterile gauze cap over the nipple which had been

put on the bottle in the diet kitchen. The nurse carried the bottle to the bedside of the mother, and the mother took off the gauze cap and popped the nipple into the baby's mouth.

This sounds simple, and it may be an old story to many of you. I assure you it is not an old story to many other persons in this country. If a better method of transferring infection from baby to baby can be devised I do not know it.

Second, I see that Dr. Butler has fed no protein milk to his babies. I have always thought it rather a good thing to give this milk after diarrhea, perhaps because it tasted so bad they took little of it. It takes a baby about three days to become so conditioned to the taste of protein milk that he will take any quantity of it. I am afraid the skimmed milk mixtures taste too good. I have never seen the advantage of using skimmed milk rather than dilutions of whole milk. Intestinal intoxication is a rare condition in private practice, although it is common in the great university hospitals and occupies the attention of the best workers we have. In the last five years I have been engaged in an active private practice. My associates and I see practically every acutely ill baby in two counties. If I remember correctly, we have seen 3 or 4 cases of intoxication in five years, and those all came from nurseries for the newborn. Babies do not have acute diarrhea as they did years ago.

Of course, our own patients with diarrhea are treated promptly so that their condition does not become intoxication, but even in the babies treated by others intoxication apparently develops rarely. I think it is a good index of the improved treatment of infants because twenty-five or more years ago that statement could not be made.

DR. KATHARINE DODD, Cincinnati: It is always a comfort to know that other people have the same trouble that I myself have. I refer to the fact that infants contract diarrhea not only outside the hospital, but also in our own wards. For a long time I have been interested in diarrhea of the newborn and have assumed that the diarrhea which spreads in our infants' ward was the same disease. Of course, until an etiologic agent has been proved, it does not necessarily follow that diarrhea in older infants is the same disorder as that which attacks the newborn.

Dr. Butler stated that in his hospital infants up to 13 months of age contract the infection. The assertion is often made that it is safe to admit newborn infants with diarrhea to an infants' ward, since the older babies are immune. I have never found this to be true. In Cincinnati, we are fearful of admitting newborn infants with diarrhea to our infants' ward. The older babies have always become ill.

I am also indebted to Dr. Smith for his talk about the care of nipples. We have been both concerned and puzzled as to how the disease is transmitted. We have one milk room where all our formulas are prepared. The disease never breaks out on our private wards. It always spreads on the general ward. Nipples, bottles and technic are the same on the two wards except that the general ward always contains some infants with the disease and the private ward seldom has infants with the disease.

With regard to Dr. Butler's remarks about hypocalcemia, the condition, as we see it, generally occurs in babies with acute diarrhea and uncommonly in infants with chronic diarrhea. We do administer sodium bicarbonate or sodium lactate as an initial procedure. Afterward, our dose of chloride is nearly the same as his. As a matter of fact, we have used his figures in calculating how much sodium chloride our infants should receive.

Has Dr. Butler observed that some infants can take a solution of dextrose and sodium chloride by mouth and yet are unable to tolerate a formula as simple as one of skimmed milk and sugar? Except when vomiting occurs, it has seemed

to me that most infants who tolerate oral administration of dextrose and saline solution can be given equally well a higher caloric mixture of skimmed milk and sugar.

DR. D. C. DARROW, New Haven, Conn.: I should like to say a word about the incidence of diarrhea in Texas. There were about 1,300 deaths per year from diarrhea in the state of Texas two or three years ago, which is higher than the number of deaths from poliomyelitis in all the United States. Texas is a big state, but still it has one of the highest death rates from diarrhea. States with higher death rates from diarrhea are Arizona and New Mexico. I figure that 1 of 30 babies born to Mexican or Negro persons in those states dies of diarrhea; while we may think the conditions that Dr. Smith had contact with in his early days in New York have disappeared, they have not disappeared in the United States as a whole.

The other fact I should like to call to your attention is that in civilized and isolated New England, and in Philadelphia, there are epidemics of diarrhea in the services for the newborn, which occur in our best-cared-for population, so that diarrhea is still one of the most important problems of pediatrics.

DR. SAMUEL KARELITZ, New York: The fact that we have gone far in the successful treatment of diarrhea becomes obvious if one visits the countries where the mortality is still 85 per cent, as I observed it to be in North Africa, where the treatment is the same as it was twenty-five years ago. On the other hand, I think we are relearning many things that we knew ten to twenty years ago.

It is gratifying to hear Dr. Butler say that the type of milk is not so important as when oral feeding is started, and the amount given. That is a conclusion which Dr. Béla Schick and I arrived at a long time ago. It has been customary for us to start feeding with an ordinary formula of two-thirds milk and 5 per cent added sugar, indiscriminately, and only occasionally did we have to change it because a possibly allergic child was in question, or one that subsequently was seen to have celiac disease. By and large, resorting to protein milk or other milk mixtures is rarely necessary.

The question of the disappearance of the disease, as Dr. Smith suggested, is, in our experience, dependent on the kind of practice one has. If one works where the economic conditions are bad, severe diarrhea is still seen, and children do become toxic and go into collapse. The disease has become continual in that type of economic environment. Its occurrence is no longer limited to the summer.

I think Dr. Darrow would have a field day if he went to North Africa and watched events after a period of sirocco. The temperature goes up to 135 F. and within the next few days the babies become dehydrated and collapse. Diarrhea is a secondary development, but the babies ultimately have the same condition that we see.

I think we are overemphasizing the nature of the fluid which we inject in the initial phase of treatment, appreciating of course that some mixtures are preferable to others. I still feel, as Dr. E. A. Park, Dr. G. F. Powers and others did, that the first thing of importance in treatment is to keep the baby alive. It can be done with salt solution, with lactated Ringer's solution U.S.P., with glucose solution, with combinations of these and with the addition of blood plasma.

We have arbitrarily set approximately 11.5 Gm., or about 80 per cent, hemoglobin on a 14.5 Gm. scale, as the level on admission above which we would not transfuse until the blood has been diluted with electrolyte solutions, because of experiences such as Dr. Butler reports, namely, cardiac decompensation due to overloading with blood. In those patients with high hemoglobin content we use plasma whenever possible or transfuse after the blood has been diluted.

I should like to report that we have had 3 patients with acute yellow atrophy, which we believe was caused by infection with plasma. In another child, the fourth, jaundice developed but the child recovered. Two of these were infants who were treated for diarrhea and dehydration.

Certainly, the mortality statistics as reported by Dr. Darrow and Dr. Butler show striking improvement, which I believe is due in great measure to what they are doing. There is no question in my mind but that their contributions are of great importance but these are not the only factors which account for the lowered mortality and I think we may not stress them beyond a given limit.

Let me point out one thing more: that physicians in a large part of this country are not equipped to do careful balance studies or even adequate chemical determinations. The type of treatment that is recommended must therefore be as simple as possible. These physicians must be guided not alone by milliequivalents of potassium or sodium, but by clinical symptomatology. They must have a form of treatment that is generally accepted and simple to administer.

DR. ALLAN M. BUTLER, Boston: We became interested in this subject because we were aware of such losses as Dr. Guest and others had pointed out previously. Therefore, we recommend giving potassium and phosphorus in our intravenous therapy. Dr. Pratt wondered whether we should have phosphorus in our fluid for parenteral administration. I have no idea whether we should have it for repair of the dehydration of diarrheal subjects. I am sure, however, that it is necessary in repair of the dehydration of diabetic coma, because glucose and insulin therapy in diabetic coma apparently creates a great demand for phosphorus, as is reflected by the pronounced fall in inorganic serum phosphorus, which persists for days. Whether we should give it to diarrheal babies or not still remains to be proved.

Dr. Smith is right, as usual. I think I can answer his question to some extent. I do not think the agent of spread is nipples. At least in this day and generation, it should not be, because nipples should not be put on bottles by nurses in the babies' room. Nipples should be put on bottles when nipples and bottles are autoclaved in the formula room. The contamination in my estimation comes largely via physicians. Of all the persons who disobey the technics of isolation precautions within hospitals physicians, I think, are the most guilty. Nurses are pretty good; but as one watches what physicians do when they go in and out of rooms, one wonders that nurses ever take precautions at all.

I think I accept Dr. Smith's explanation of the ineffectiveness of protein milk. I agree with him about the disease being to a considerable extent a hospital infection. Dr. James L. Wilson and myself are the only two persons who, consistently, at meetings of the Children's Bureau of the United States Department of Labor, at Washington, D. C., with the obstetricians, refuse to endorse the principle that all babies should be delivered in hospitals. We do so because of the infectious diarrhea of the newborn which occurs in hospitals and which in the past has carried such a high mortality.

We tried to define our disease by saying it was persistent nonbacterial infectious diarrhea. We are not as capable as Dr. G. J. Buddingh and Dr. Dodd in identification of virus disease, so we did not wish in any way to say this was Dodd-Buddingh virus disease. We know only that our disease was not associated with any bacterial infection.

Dr. Dodd raised a question about the giving of dextrose and saline solution orally. My answer would be: The ordinary 5 or 10 per cent dextrose in isotonic sodium chloride solution should not be used as oral therapy. Isotonic sodium

chloride solution given into the gastrointestinal tract when it is empty is a cathartic. I think a solution such as we, or Dr. Darrow, have been using in oral therapy is much better.

I doubt that I can agree with Dr. Karelitz as to the use of hemoglobin as an index of transfusion. Transfusion appears to be good therapy for a dehydrated baby in certain circumstances, even if the hemoglobin level is high. As the result of transfusion under such conditions, the hemoglobin content will usually fall.

The balance studies that are being conducted on this condition are not designed to complicate therapy. They are studies which are leading to information that has simplified therapy. The results of treatment in the cases reported by our group this morning are evidence of the fact that balance studies are leading to simplification, not complication, of therapy.

Erythroblastosis Fetalis Treated by Replacement Transfusion via the Umbilical Vein. DR. LOUIS K. DIAMOND, Boston.

The treatment of erythroblastosis fetalis has changed considerably in the fifteen years since my associates and I published our first series of such cases. As a result, there has been a slow but steady improvement in the figures for mortality from this disease.

Originally, treatment consisted merely of transfusion of whole blood as needed for developing anemia. Usually, the father's blood was used, which meant Rh-positive blood. The mortality then was about 40 per cent.

After 1941, when the Rh factor was recognized, it was logical to change to transfusion with only Rh-negative blood. Some of the sicker children were undoubtedly saved by this procedure. Gross mortality figures now showed about 30 per cent deaths. Evidence accumulated by our laboratory and by many others proved that Rh-positive cells given to newborn infants with severe hemolytic disease are destroyed faster, produce more jaundice and, occasionally, cause collapse of the patient. We have seen 4 such cases. Mildly erythroblastotic infants may recover even with transfusions of Rh-positive blood, but Rh-negative blood is by far the safest and should be the only type used.

Since many infants with erythroblastosis are severely affected at birth, or even stillborn, it seemed logical to introduce one further step in modifying the disease. This consisted of delivery two to three weeks before term in women with a demonstrably high or increasing titer of anti-Rh agglutinins, especially when they had lost previous children from the disease. This further reduced the mortality rate to 20 per cent.

Finally, since some of the infants born alive to mothers having much Rh antibody looked well for twenty-four hours or more but then suddenly became sick, it seemed necesary to do something further. By routine tests it was found that most such ill children had appreciable amounts of passively transferred antibodies in their cord or peripheral blood serum at birth and a preponderance of bound or "blocked" red cells. Therefore, replacement transfusions seemed indicated.

Our first few patients so treated offered considerable difficulty. The longitudinal sinus may not be readily located shortly after birth because of molding of the head. It is a dangerous vessel to puncture blindly. Peripheral veins and arteries are difficult to enter without careful dissection by experts, the vessels are thin and fragile and cannulas clog easily. Heparinization to prevent clogging may be dangerous at this period of life. The exposure of the newborn infant to two hours of surgical manipulation on an operating table may be a shocking procedure.

Through the cooperation of our neurosurgeon, Dr. F. D. Ingraham, thin-walled plastic catheters were obtained. These are made of polyvinal and are flexible

and nonirritating to nerve or vascular tissues, even for many hours. Blood does not clot in them too readily. The umbilical vein lends itself to easy passage of such catheters for the first twelve hours or more of life.

The patients to be treated by replacement transfusion are selected on the basis of (*a*) visible clinical manifestations of hemolytic disease at birth or shortly thereafter, and if no such signs occur, on the basis of (*b*) laboratory tests proving that the mother has an important amount of Rh antibody or that her infant has Rh-positive cells, free antibody in its circulation and/or bound cells.

The method of treatment can best be illustrated by lantern slides. There are several important safeguards for the success of the operation. The infant should be warm and kept so. A Hess bed is our recommended operating table. The airway must be cleared and suction used on the larynx and throat as needed. Oxygen is administered constantly. The blood for transfusion should be compatible, Rh negative or group O in type and neutralized with A and B substances. It should be warmed to body temperature.

Test samples are taken three or four times during the process of removing the infant's blood. Five hundred to 1,000 cc. of blood is used for the transfusion. At the end of the operation, 6 to 10 cc. of 10 per cent solution of calcium chloride is injected intravenously. The infant is given penicillin and sulfadiazine prophylactically for forty-eight hours and fed cautiously at first and not too early.

The results have been encouraging in our first 50 cases. The mortality has been about 10 per cent. About 8 individual cases have been truly dramatic. Of the infants all but 3 were discharged home with the mother. The incidence of kernicterus has not seemed to be affected up to the present.

The need for good judgment and careful pediatric supervision of the infant with erythroblastosis fetalis is greater than ever. Overenthusiasm may harm more infants than the treatment may save. We already have encountered too many babies who received unnecessary transfusions. The present mode of treatment offers an improvement in the technic and simplicity of replacement transfusion rather than a panacea for all erythroblastotic babies.

DISCUSSION

DR. GEORGE M. GUEST, Cincinnati: I should like to ask Dr. Diamond if the plastic catheters he uses are now available to other investigators. How early does he recommend delivery of infants in whom erythroblastosis is expected?

DR. CARL H. SMITH, New York: Of the several methods that have recently been advocated for substitution or exchange transfusions in erythroblastosis fetalis, that described by Dr. Diamond employing the umbilical vein appears most attractive because of its simplicity. With the growing emphasis on the desirability of replacing the Rh-positive blood of the affected infant with Rh-negative blood, this procedure or one of its modifications should become increasingly popular. Since replacement transfusions involve an element of risk in the treatment of infants immediatly after birth, it is obviously important to establish criteria for the choice of patients.

In recent years attempts have been made to prognosticate the type and severity of erythroblastosis in the newborn infant from the results of serologic tests in the mother during pregnancy, from the hematologic picture and, to a lesser extent, from the results of serologic tests in the infant. Correlations thus far have been confusing, yet it is the appraisal of these data that provides the indications for a procedure in which few persons are relatively expert at present.

The opinion of Dr. Diamond on some of the current problems relating to the indications for replacement transfusions would be extremely interesting and

valuable. The significance of increasing agglutinin titer in the mother and the differentiation between agglutinin and blocking antibody in relation to the clinical type of erythroblastosis at birth have been the subjects of considerable discussion. Can any relation be established between the titer of either of these antibodies in the mother and the type of infant who is not anemic at birth but in whom the progress of the disease is swift and often fatal? If the presence of either, or both, of these antibodies in the mother is significant, what is the critical level for advising replacement transfusion in the infant? It would be expected that the most important single criterion for this procedure is the presence of antibodies in the cord blood and evidences of in vivo isosensitization in the infant. Is it necessary, therefore, as a prime indication to detect sensitized cells in the baby and, if so, what technic is suggested for this determination?

Finally, with replacement of the blood as completely as possible, do these babies eventually become anemic again to the extent of requiring subsequent transfusions? If this phenomenon is at all common, it would suggest that antibodies are present in tissue reservoirs and in body fluids and are not completely drained by the present specifications for replacement transfusion. I know that Dr. Diamond has had wide experience in this field, and I would appreciate his comments on these puzzling aspects of this disease.

DR. ARNOLD L. GESELL, New Haven, Conn: Are there any data on neurologic complications?

DR. SAMUEL KARELITZ, New York: Dr. Diamond, in doing the exsanguination transfusion do you attempt to keep the hemoglobin concentration up to about 120 per cent or do you, after completing the transfusion, lower the hemoglobin level to about 90 per cent and the cell count to about 4,500,000 red blood cells? If that has been done, have you noted any effect on the subsequent development of jaundice?

DR. LOUIS K. DIAMOND, Boston: In answer to Dr. Guest's question, these catheters have been made for Dr. Ingraham and for us by a plastic manufacturing concern in Clinton, Mass. This is a small item in the business of the concern, which primarily manufactures plastic insulation material for wires used in radar and radio instruments. Since the concern manufactures several hundred thousand feet per week, 10 or 100 feet (3 or 30 meters), such as any one clinic might need for several years, is too small an item for it to bother with. In addition, the manufacturer has been somewhat worried about the biologic tests that Dr. Ingraham and his group, and we, have found necessary to carry out on the catheters; that is, the catheters are implanted into animal tissues, both nerve tissues and vascular systems, for a matter of several days to prove that they do not cause phlebitis or irritation. At present it has been worked out as a better method of distribution for us to buy lots of 2,000 to 5,000 feet (610 to 1,524 meters) and test each lot. We shall be glad to distribute the tubing for the time being at a small cost. I do not know its price; at any rate, 2 or 3 feet (60 or 90 cm.) will last any one physician for several months.

The best time of delivery for a woman who has anti-Rh agglutinins should be when the baby is viable, that is, large enough to live, according to the obstetrician's palpation and, possibly, roentgenographic examination, and yet not so near term as to run the risk of severer erythroblastosis. In the average case we find this is after thirty-seven or thirty-eight weeks of gestation, but not before the thirty-six weeks.

Of the 6 children who died during or immediately after replacement transfusion, 4 died from complications of prematurity, that is, atelectasis of the lungs or hemorrhages in various parts of the body, or, in 1 case, from a congenital

malformation, which may have had nothing to do with this process. We believe that immaturity may be a greater danger than erythroblastosis. We like to wait until the baby is within two to three weeks of term, and then the obstetricians must decide when they can safely deliver the baby. We do not force the issue in any case.

Another safe rule adopted by the obstetrician is that labor shall not be induced in any woman if she has 3 or more living children. In that case her life is more important than the possibility of saving the erythroblastotic baby. This is the result of a sad experience in which labor in a middle-aged woman with 5 living children, who, in addition, had lost 4 babies with erythroblastosis, was induced after the thirty-sixth week of her tenth pregnancy. She did not go into labor after rupture of the membranes, and two weeks later she died of puerperal sepsis, as did the baby, of infection of the uterus. One should not force the obstetrician's hand in any case.

Dr. Carl Smith asked about the criteria for the replacement treatment. The first and most important one is that the baby shows at delivery or shortly thereafter signs of full-blown erythroblastosis, i. e., jaundice, anemia, splenomegaly, hepatomegaly and many nucleated erythrocytes in the peripheral blood. We have observed, within the past few years, that any baby showing these signs at birth will not do well through watchful waiting or small transfusions of Rh-negative blood. Such babies in the past have died, and we feel they should be treated immediately. If the baby looks well, but we can demonstrate that its own red cells are Rh positive, that the mother has an appreciable titer of anti-Rh agglutinin (a titer demonstrated in a dilution of 1:16 or better; with titers under 1:16 evidence of development of erythroblastosis in the baby was rare) and that the baby's cord serum contains free antibody, passively transferred from the mother, the second important criterion for replacement transfusion is regarded as fulfilled.

From our experience in the last two years, with more than 200 babies tested at birth or shortly thereafter, we know these children, on the average, will not do well. Therefore, we feel that even if it looks fine at birth the presence of free antibody in a baby with Rh-positive blood, whose cells can be destroyed by this antibody, is an indication for replacement transfusion within the next six to twelve hours. One should not hasten to treat the baby before it is adequately warmed or before its airway is cleared or its color is good, because it may do badly in the midst of the treatment.

It makes no difference whether the mother's antibodies are of the so-called "blocking" or hyperimmune variety or of the simple agglutinin type. I stress this point because our laboratory tests time and time again fail to reveal which type, if not both types, of antibody is present; that is, the presence of "blocking" antibodies often obscures the ordinary, simple agglutinins. We have mixed, in test tubes, known amounts of each type of antibody and have observed that one cannot detect the titer of either accurately. It is more important, therefore, to depend on the detection of antibody in the baby's serum and the presence of symptoms in the baby rather than on what the mother shows before or immediately after the birth. These are the important laboratory procedures that determine when to and when not to treat the baby.

As to the dependence of the symptoms on the type of antibody in the mother, again we fail to find any close correlation. The mother may have a high titer of "blocking" antibody, and the baby may fail to show much erythroblastosis at birth and may fail to have any free antibody in its serum. It will then do fairly well. On the other hand, the baby's serum may contain antibody when the mother has a low titer of either the "blocking" antibody or the simple agglutinins.

After replacement transfusion, we have been able to send most of the babies home within a week; however, many of them have had a mild degree of anemia at the second to the third week—anemia as measured by levels of 3,000,000 to 3,500,000 red blood cells, with a hemoglobin content of about 70 per cent. Only in 2 of 50 babies has retransfusion been necessary at about the third week, because the babies' blood level had fallen to 2,500,000 cells or less and they were not building blood well, as evidenced by low reticulocyte counts.

We have been disappointed in observing that in the usual 16 to 20 per cent of the babies severely jaundiced at birth, or in the first twelve hours of life, kernicterus has developed. Of the 6 deaths, pathologically, 3 were due to kernicterus, demonstrated in examination of the brain. Of the living children, we have seen the usual though low average of neurologic damage. It is our feeling at present that replacement transfusion does not eliminate kernicterus or repair damage to the brain which may have occurred in interuterine life or in the first few hours after birth; however, in none of our babies has severe jaundice developed after the replacement transfusion and the removal of most of the free antibodies.

Infantile Diabetes Mellitus: Three Cases in Successive Siblings, Two with Onset at Three Months of Age and One at Nine Days of Age. DR. G. M. GUEST, Cincinnati.

The parents of the infants reported on were nondiabetic, but there was history of diabetes in branches of both families. Their first-born child was nondiabetic, a healthy girl, now 9 years of age. The second-born, a girl, was apparently well until the age of 3 months when she was admitted to the hospital with severe diabetic acidosis of probably more than forty-eight hours' duration before appropriate treatment was started; she died. The next child, a boy, was apparently well until the age of 3 months when the parents noticed polyuria and brought him to the hospital, where glycosuria and hyperglycemia, with mild acetonuria, were demonstrated. He was given a normal infant diet, with insulin dose regulated at home to permit moderate glycosuria most of the time but with precautions to avoid acetonuria. Now 20 months of age, he has progressed well, with no acute complications of the disease even during several episodes of minor infections of the respiratory tract. The fourth infant, a boy, was born at home Jan. 3, 1947 and was breast fed. Tests made by the parents showed the urine to be free of sugar for eight days. Glycosuria first appeared on the ninth day. When he was brought to the hospital on the tenth day the blood sugar varied from 250 to 650 mg. per hundred cubic centimeters during a period before insulin was administered. There was a trace of acetonuria. Three U. S. P. insulin units of protamine zinc-insulin injection U. S. P. decreased the blood sugar in twenty-four hours to approximately 150 mg. per hundred cubic centimeters. The baby was sent home on the fourth day from the hospital. He received 1 unit of protamine zinc-insulin injection daily and was breast fed. On a demand schedule he was satisfied with four feedings a day at the age of 3 months; he slept through the night and gained approximately 1 ounce (28 Gm.) each day. At 4 months of age his weight was 13 pounds 10 ounces (6,180 Gm.), and he was receiving 2 to 5 units of protamine zinc-insulin injection daily.

Our scheme for the management of young diabetic patients is increasingly free, allowing the children to eat according to appetite within approximately the same limits of choice as nondiabetic children are allowed. Dose of insulin is adjusted to permit continuous mild hyperglycemia and glycosuria, with precautions to avoid excessive glycosuria with attendant polyuria and, especially, to avoid

acetonuria. Frequent testing for acetone in the urine at home is insisted on as a most important aid to the regulation of insulin dose. Analysis of diet-diary records kept occasionally by the mothers shows that the children spontaneously adjust to an intake of food that differs little, if any, from the measured diets that were prescribed before this freer regimen was adopted in our clinic. Our experience to date indicates that the infants and children on this regimen are growing well, with minimal ill health. Hypoglycemic reactions of all degrees are rare, and emotional disturbances ascribable to mild hypoglycemia are noticeably less among the diabetic children on this regimen than among those who in former years were kept on a measured diet with insulin dose adjusted to keep glycosuria absent or minimal.

DISCUSSION

DR. JULIAN D. BOYD, Iowa City: I cannot agree with Dr. Guest in regard to the philosophy of management of diabetes in children through the period of growth and development. During the past twenty years my associates and I have followed the course of at least 400 children with diabetes mellitus, and we have seen many patients grow to adulthood. Our observations included the social, emotional and educational course of these patients, as well as their strictly medical status. We believe that the goal of the physician and of the family should be the closest approximation to a good physiologic level of management that circumstances will permit.

The easiest type of diabetic care to institute at the outset of management is the one which requires the least from the patient and his family. Such a level of management also is simplest at the outset for the physician in charge. It is easy to make the family feel happy and temporarily secure with a mediocre type of care. The ultimate risks of such management cannot be detected until emergency arises or until the passage of years reveals the defects of poor control.

Our studies indicated that it is not difficult to establish a state of essential aglycosuria and to maintain it with fair constancy for periods of years. It is equally easy to meet completely all the nutritional requirements of the diabetic child throughout his period of growth, without resort to distasteful or unnatural diets. Children so controlled are healthy, free from diabetic emergencies and from degenerative diseases and happy. The diabetic routine of itself is not a cause for discontent or for unhappiness due to self denial, if a proper emotional state is fostered by the physician and by the parents. Once our patients have adapted themselves to a physiologic routine, they are unwilling to experiment with laxer methods of control. The progressive requirement for insulin for such patients is lower than for poorly controlled patients.

When diabetic children first come under our care after several years of poor management, we have great difficulty in attaining stability and constancy of insulin dose. The ultimate insulin requirement often is high, and the prospects for maintaining aglycosuria are lessened. It seems important to us to establish rigid control at the outset, rather than to be forced to do so after a lapse of months during which the patient's resources have been drained.

We do not restrict our patients' diets as much as one might infer from what Dr. Guest has said. We calculate the needs of the individual child and then meet them fully, so fully that the child has no desire for additional food. The intake is fully regimented; we prescribe the specific foodstuff both as to nature and as to amount. The three meals are isocaloric: the proportionate insulin need can be predicted throughout the day because of this constancy of intake. The foods used are easily available and no more expensive than those recommended for the non-

diabetic child: milk, meat, eggs, vegetables and fruits, and the usual accessories, comprise the menus. We believe that by example these children have served to improve the diets of the other members of their families, with favorable results for their siblings.

The countenance of continuous glycosuria seems parallel to the condonation of continuous dyspnea in a patient with cardiac failure. Both glycosuria and cardiac dyspnea represent manifestations of decompensation of a vital function. Such decompensation does not develop until the body's compensatory mechanisms have attempted to correct the underlying organic defect and failed. By maintenance of aglycosuria the exhaustion component of the insulin deficit is avoided, and one needs supply only the amount which the organism intrinsically requires beyond its own capacity for production.

Few families will observe a stricter regimen than that their physician imposes; most will fail in some measure to meet the prescribed routine. Such being the case, it is important that the physician set his sights at the best possible objective, rather than at one which is inferior in its prospects for prolonged well-being.

DR. GEORGE M. GUEST, Cincinnati: We all admire the success Dr. Boyd and Dr. R. L. Jackson have had in their clinic at the Iowa Children's Hospital with their carefully regimented scheme of diabetic care. I am sure they have attained a nice degree of regulation of their patients, with normal glycemia and aglycosuria, such as is rarely attained elsewhere. Many of us here, however, have admitted defeat in attempts at such close regulation and have had to compromise by adopting a more easily practicable regimen even when subscribing to the theory that aglycosuria may be most desirable. All advantages of a freer regimen, from the point of view of parents, as well as of patients, must be weighed against the theoretic objections that are raised against it.

There is general agreement that the young diabetic patient's diet, whether measured or unmeasured, must correspond essentially to that of a nondiabetic normal child and must satisfy all the demands for energy and growth. The question of the asserted harmfulness of hyperglycemia per se is the crux of the debate over the free-diet-glycosuric regimen. I should like to cite the classic experiment done a few years ago by Dr. I. A. Mirsky and Dr. W. E. Nelson in Cincinnati, which demonstrated fairly conclusively that even an extreme degree of hyperglycemia resulting from an excessive intake of carbohydrate does not of itself precipitate acidosis and coma, if the minimal amounts of insulin that are required to avoid ketosis are supplied. A boy 15 years of age was maintained on an extremely high carbohydrate diet, with his blood sugar level constantly between 600 and 1,000 mg. per hundred cubic centimeters for two weeks without apparent ill effects. Of course, this is not a procedure recommended for care of diabetic patients; but the experiment refutes the claim that glycosuria in the diabetic patient is a sign of a grossly unphysiologic state comparable to cardiac decompensation, and such observations engender confidence that even a considerable degree of glycosuria is not immediately harmful. A more important question is whether the late complications of diabetes, e. g., those of degenerative cardiovascular disease, will be aggravated by long-continued hyperglycemia. Experiences reported from the Scandinavian countries, where the free dietary regimen has been followed longest, afford considerable evidence that the late complications of diabetes are not greater among the patients so treated than among those cared for by more conservative methods. Perhaps still longer experience is needed before definitive conclusions can be drawn, but the evidence now available certainly justifies a thorough trial of the freer regimen since, if feasible, it is undeniably a boon to all persons concerned.

DR. WALDO E. NELSON, Philadelphia: I should like to clarify certain implications in regard to the observations of my associate and me on diabetic children who were given exceedingly high carbohydrate diets. These diets contained carbohydrate in amounts ranging from 500 to 880 Gm. per day. Such diets were not without ill effects. The resulting blood sugar levels were as high as 600 to 1,000 mg. per hundred cubic centimeters, and, when children were kept on such regimens for periods from a week to thirty days, they did lose weight. The point at issue, which Dr. Guest has interpreted correctly, was simply whether excessive carbohydrate intake was a contributory factor to the development of acidosis. Under the conditions of the experiment there was no increased acetonuria but rather a decrease, and no tendency toward acidosis. However, such diets are under no circumstances to be considered as ideal for treatment.

It would seem that the situation is somewhat as it is in the field of diarrheal problems, where there is also a definite need for control studies. Those of us who are interested in this field, rather than comparing one regimen with another, have more or less followed a given plan of management with which we have had reasonable success. The point that Dr. Boyd has made, namely, the treatment of the total child, is an important one, with which Dr. Guest and others of us are in complete agreement. As to the question of the possible harm of continued hyperglycemia, one must give attention to the studies of Haist and Best and of Lukens and Dohan on the one hand and to those of Mirsky and N. A. Nelson on the other. and, until there is clarification of what the effects of hyperglycemia may be on body structures, it would seem that we have no clear basis of reference.

Comparative Absorption, Excretion and Storage of Oily and Aqueous Preparations of Vitamin A. DR. J. M. LEWIS, DR. OSCAR BODANSKY, DR. J. BIRMINGHAM and DR. S. Q. COHLAN, New York.

A comparison of the vitamin A concentration in the blood following administration of oily (percomorph liver oil N. N. R.) and aqueous preparations was carried out on infants and children. Blood levels were determined three, six, nine and twenty-four hours after the administration of 5,000 units of vitamin A per pound (0.5 Kg.) of body weight. The results of this experiment revealed significantly higher concentrations of vitamin A in the blood after the administration of the aqueous preparation. We obtained similar results in adults.

In order to determine the significance of these differences in blood levels following oily and aqueous preparations of vitamin A, fecal excretion was studied in 7 infants. It was observed that the average fecal excretion of vitamin A following the administration of the oily product was 38 per cent of the amount ingested, whereas only 7 per cent was excreted with the administration of the aqueous preparation. These results indicated that the oily preparation was poorly absorbed, while the aqueous preparation was well absorbed. Thus, it may be concluded that the difference in blood levels obtained after the administration of these preparations was due to a pronounced difference in the absorption of vitamin A from the intestinal tract. Experiments in rats and guinea pigs also revealed that the blood levels of vitamin A were higher and the fecal excretion lower with the administration of the aqueous preparation. Furthermore, the storage of the vitamin in the liver was much higher when the aqueous preparation was given.

The aqueous preparation contained vitamin A alcohol dispersed in a watery solution of propylene glycol N. F., whereas the oily product consisted of vitamin A esters of the higher fatty acid groups dissolved in fish liver oil. Another difference between these two types of vitamin A preparations was the presence in the aqueous

product of vitamin A components, ascorbic acid and a solubilizer, mannitan monolaurate.

The question arose whether the better absorption of the aqueous preparation was due to the presence of vitamin A alcohol. Experiments carried out in rats, guinea pigs and infants failed to disclose any difference in the absorption of vitamin A alcohol and vitamin A esters when dispersed in the same vehicle. Furthermore, the presence of vitamin B components in ascorbic acid played no role in the superior absorption of the aqueous preparation. The solubilizer, mannitan monolaurate, however, was an important factor, as the blood levels of vitamin A and the stores in the liver were much lower in rats and guinea pigs after the administration of the propylene glycol solution of vitamin A containing no solubilizer.

The aqueous preparation which we employed in this study contained 47 per cent propylene glycol and 53 per cent water. When the vitamin was dispersed in 100 per cent propylene glycol or 100 per cent water, the blood levels of vitamin A and the stores in the liver were significantly lower than were obtained with the preparation containing 47 per cent propylene glycol.

In a recent experiment a preparation of vitamin A esters dispersed in an aqueous solution of "dextri-maltose" was given to rats and children and the resulting blood levels were just as high as those obtained after the administration of vitamin A alcohol in 47 per cent solution of propylene glycol.

DISCUSSION

DR. BENJAMIN KRAMER, Brooklyn: The interest of my associates and me in this subject arose from the observation that the intramuscular administration of vitamin A in oil is not followed by an elevation of the vitamin A level in the blood. It was rather surprising to us because Dr. A. B. McCoord had reported that in dogs there is a rise in the vitamin A level following the administration of vitamin A ester in oil. We repeated this determination on several occasions and invariably obtained the same result. These studies first were made on children with cystic fibrosis of the pancreas or some other condition in which vitamin A absorption from the gastrointestinal tract was much impaired.

When we determined vitamin A levels for normal children, the result was the same. We then tried a watery dispersion of vitamin A and found a definite elevation in the blood level, although the rise began to occur rather late as compared with the elevation in normal children when the vitamin dispersed in oil was given by mouth.

[Slide] The lower curve on the slide is one obtained for a child given vitamin A in oil intramuscularly; the second curve was obtained with the intramuscular administration of vitamin A dispersed in an aqueous medium.

[Slide] Four children who had clinical evidence of celiac syndrome and who had low curves for vitamin A were given the vitamin. Over a period of nine hours, there was little rise in the vitamin A level. This was followed over a longer period with a similar or the same result in some of the patients. After the oral administration of the aqueous dispersion, there was a definite rise in the vitamin A level at the end of the third hour and a return almost to the normal level at the end of the ninth hour.

[Slide] From normal children similarly treated, we obtained, as did Dr. Lewis, the striking difference in the curves for vitamin A given in oil and as the watery or the aqueous dispersion.

I may say that the curve for vitamin A in oil is low in young infants and in persons with mongolism. In the normal children, in the normal older children

as well as in normal infants, and in those with mongolism, the vitamin A level is elevated as indicated here, though not always to the same degree.

[Slide] We then tried a watery dispersion from which the other vitamins were removed and obtained a much better, much higher curve with the simple suspension of the vitamin A in the watery medium.

[Slide] These are results of a control study to show that the medium itself, when administered in the same quantity, has no effect whatsoever on the vitamin A level.

[Slide] This study showed that the storage of vitamin A in the liver following the administration of the two aqueous dispersions containing different amounts of the dispensing agents, with or without other vitamins, is higher than when vitamin A is given in corn oil U. S. P. Is not the larger amount of vitamin A found in the stool a result of a protection of the vitamin by the oil against oxidation in the gastrointestinal tract? That protection probably does not account for all the increase, but does it not account for some of the increase?

DR. STEWART H. CLIFFORD, Brookline, Mass.: My colleagues and I became interested in this problem in an effort to discover whether a lack of vitamin A could be a factor in the development of retrolental fibroplasia in the premature infant. Our interest was aroused by the results of the animal experiments of Dr. Josef Warkany that were reported before this society.

Last year at the meeting of the Society for Pediatric Research, we announced we could find practically no absorption of vitamin A in the premature infant when the vitamin was given in an oily form, but a satisfactory curve for vitamin A absorption could be obtained when the vitamin was provided in an aqueous preparation, a water-soluble form.

At that time, similar observations were made as to the absorption of vitamin A in an aqueous solution in infants with pancreatic fibrosis and also in those with chronic infections, which are accompanied with a low absorption curve for vitamin A when an oily vehicle is used.

Unfortunately, we must announce that even when vitamin A was given to premature infants in a soluble form it had no effect on the subsequent occurrence of retrolental fibroplasia.

I should like to ask Dr. Lewis whether it is reasonable to assume that the absorption of vitamin D will parallel the absorption curve discovered for vitamin A in individual patients, so that vitamin A could be used as a marker for vitamin D absorption.

DR. PHILIP C. JEANS, Iowa City: Relative to the concentrations of vitamin A in oil and in water, were they the same?

DR. J. M. LEWIS, New York: In answer to Dr. Kramer's question as to the reason for the large amount of vitamin A in the stools when the oil was administered, I would assume that the oil was poorly absorbed and carried with it the vitamin A. The mechanism responsible for the poor absorption of the oily as compared with the aqueous vehicle is a problem which requires investigation.

In reply to Dr. Clifford's question of whether absorption of vitamin D would be enhanced if it were administered in an aqueous vehicle, some years ago we observed that vitamin D dissolved in propylene glycol and dispersed in milk was more effective in the prevention and cure of rickets than vitamin D administered in an oily vehicle. Therefore, it seems likely that vitamin D administered in an oily vehicle is not so well absorbed as that given in an aqueous vehicle. Unfortunately, there is no chemical method of determining the vitamin D concentration in the blood, so that one cannot compare the blood levels of vitamin D administered

in oily and in aqueous vehicles following the administration of a large dose of vitamin D. There is a biologic method for assaying the vitamin D content of blood, but this procedure is extremely laborious.

Dr. Jeans inquires as to the vitamin A concentration in the oily and aqueous preparations. The aqueous preparation contained 10,000 units of vitamin A per cubic centimeter, and the oily preparation, which contained 60,000 units per cubic centimeter, was diluted with cottonseed oil in order to make the potency comparable to that of the aqueous preparation, namely, 10,000 units per cubic centimeter. I might add, however, that a comparison of the absorption of diluted and undiluted oily preparations of vitamin A, employing the same number of units, of course, revealed no difference in absorption of the vitamin in guinea pigs and in rats.

Dental Caries as Modified by Institutional Life. Dr. Julian D. Boyd and Dr. Virgil D. Cheyne (D.D.S), Iowa City.

The incidence and extent of caries was measured among the children resident in six custodial institutions. The individual scores for caries were compared with the average values reported for a general school population. Among the younger subjects, the institutionalized children exhibited a higher incidence of caries than did the control group, but during the adolescent years caries were notably less among the children living under institutional regimentation. There were the least caries among those who had lived the longest periods in the institution. No difference as to sex in incidence of caries was evident. There was no relation between the amount of therapeutic or prophylactic dental care the children had received and their respective scores for caries: the majority of the children examined had never received professional dental care, and many showed evidences of prolonged neglect of oral hygiene.

The data support the thesis that regimentation of living conditions modifies caries experience, without relation to the intraoral environmental factors. There was no evidence that posteruptive ingestion of fluorine bore a relation to the lessening of caries among these children. Of the conditions which institutional life imposes, the nature and regimentation of the diet seemed to be the only one which may have modified the course of caries of these subjects significantly. The institutional diets were ample in their content of milk, meat and vegetables. Carbohydrate foods had provided most of the energy value of the diets; consumption of sugar had not differed greatly if at all from that which is customary for the average child. The study is offered as a record of what one may expect to find in the mouths of a specific child population.

Surgical Treatment for Coarctation of the Aorta. Dr. Robert E. Gross, Boston.

The prognosis for patients with coarctation of the aorta is discussed. In general, this congenital abnormality seldom causes disability in the childhood period, but it is apt to give rise to important symptoms or even to fatal complications in early adult life. The features in diagnosis of the condition are reviewed. A surgical technic has been developed for correction of this vascular malformation; this consists of removal of the narrowed segment of aorta and anastomosis of the remaining aortic ends. This procedure was developed by practice on animals, and it has now been adopted for use in human beings. The results of 18 such operations are discussed, with particular reference to the lowering of hypertension in these subjects. For technical reasons it is almost impossible to perform this operation in adults; hence it is important to recognize the lesion in childhood when the blood vessels are still in a state which will allow this surgical treatment.

Abscess of Brain: A Complication of Congenital Heart Disease (Tetralogy of Fallot). DR. ALFRED HAND, Philadelphia.

This combination of defects of the heart and brain, having formerly received scant recognition, is being mentioned in medical literature with increasing frequency. Dr. S. L. Robbins in 1945 found a total of 26 cases including 3 of his own. Among these cases were only 3 in which the abscess had been diagnosed with subsequent operation, resulting in 1 recovery. I wish to report 2 cases, 1 of my own and 1 from the service of Dr. Francis C. Grant in the Department of Neurosurgery of the Hospital of the University of Pennsylvania, Philadelphia. Both these patients died. Dr. Grant's patient recovered after the first operation, but a second abscess developed, with general meningitis, causing death. Another case in which diagnosis was made, with operation and recovery, was reported by Smolik, Blattner and Heys (Brain Abscess Associated with Congenital Heart Disease: Report of Case with Complete Recovery, *J. A. M. A.* **130**:145-147 [Jan. 19] 1946), making a total of 6 in which operations were performed, with 2 recoveries. With Dr. Robbins's 26 cases, these 3, with 5 others found in the literature in which the abscesses were observed post mortem, make a total of 34; since presenting this paper, I received a personal communication from a fellow practitioner regarding an unreported case, which brings the total to 35 cases.

These 35 cases of brain abscess complicating congenital heart disease, when considered with the infrequent occurrence of the latter in the average run of medical practice, justify the belief that patients with congenital heart disease as a class have greater susceptibility to this complication than all the other medical groups of children, even those with otitis or acquired cardiac lesions. This susceptibility should receive greater attention in medical literature and educaton, especially in courses in pediatrics, internal medicine, neurology and surgery.

The caretakers of such a patient should be told of this susceptibility and advised to watch in any acute illness for unusual symptoms referable to the nervous system. The patient himself, if he reaches adult life, should also be told, as tactfully as possible, that if he gets sick in any way and any new symptoms, such as localized headache, neuralgia in one spot, muscular twitchings or disturbance of vision develops to report it at once to the physician; he should, however, dismiss from his mind all thought of these as long as he is well.

All those patients in whom the existence of pulmonary stenosis, a defect of the ventricular septum or patulous ductus arteriosus is definitely proved or even suspected should be examined by a surgeon especially trained in the new and marvelous surgical procedures for the closing of a patent ductus or for anastomosis of the pulmonary artery with the aorta or one of its branches. The improvement in oxygenation after anastomosis favors improvement in the general health, even if the procedure may not lessen the possibility of paradoxic embolism. The operation for occlusion of the ductus has been advocated to overcome the tendency to endocarditis or endarteritis which these patients show in adult life; it will certainly remove the possibility of brain abscess by paradoxic embolism. Therefore, this treatment seems to be strongly indicated in all these patients, unless some equally strong contraindication is present.

Analysis of the First 350 Patients Operated on for Pulmonary Stenosis or Atresia. DR. HELEN B. TAUSSIG, Baltimore.

An analysis of the first 350 patients subjected to operation for pulmonary stenosis or atresia showed that 90 per cent had clinical evidence of tetralogy of Fallot and 10 per cent had other malformations.

Among the patients whose condition was diagnosed as tetralogy of Fallot, the mortality rate was 14.5 per cent. When, however, the subclavian artery was used for repair instead of the innominate or carotid artery, the mortality rate was 7 per cent. The errors in diagnosis were 5 per cent; the commonest one concerned the pulmonary artery.

Thirty-seven other patients with pulmonary stenosis or atresia were operated on; the mortality rate in this group was 30 per cent. These patients may be divided as follows: Fifteen patients in whom electrocardiograms showed a left axis deviation were operated on with but 2 deaths, that is, a mortality rate of 13.3 per cent. Ten patients had dextrocardia with or without situs inversus; in this group there were 3 deaths. Three patients showed left axis deviation and nodal rhythm; 2 died at or immediately after operation. In both instances death appeared to be due to an inability of the heart to accelerate. Three patients showed slight rotation of the heart on its axis; of these 2 died at operation. Three other patients had clinical evidence of pulmonary atresia or extreme stenosis and a defect of the auricular septum, as determined by catheterization of the heart. Two were greatly improved by operation. Three had situs inversus with levocardia; 1 died.

In patients who did not have typical tetralogy of Fallot no effort was made to arrive at a correct anatomic diagnosis; attention was directed to the criteria essential to successful operation. These criteria are:

1. The primary condition must be lack of adequate pulmonary blood flow.
2. A pulmonary artery must be present to which to anastomose the systemic artery.
3. A systemic artery must be available.
4. The difference in pressure between the systemic circulation and the pulmonary circulation must be such that blood will flow from the aorta to the lungs, that is, pulmonary pressure must be low.
5. The structure of the pulmonary artery and the lungs must be such that the patient can survive the collapse of one lung and the temporary occlusion of one pulmonary artery.
6. The structure of the heart must be such that it can adjust to the altered circulation.

The most important considerations are the cardiac reserve and the direction of both venous blood and oxygenated blood to the aorta. The cardiac reserve can be estimated by the size of the heart. If the heart is normal in size, the probability is that the reserve is good. Determination of the circulation time is the simplest test to ascertain whether venous blood is directed to the aorta. Venous blood must reach the aorta because it is the direction of venous blood to the lungs through the artificial ductus arteriosus which is beneficial. The ease with which oxygenated blood is directed to the aorta is extremely difficult to determine prior to operation.

In summary, in children with tetralogy of Fallot the operative risk is less than 10 per cent. In patients who have other malformations and evidence of pulmonary stenosis or atresia, the mortality rate is still 30 per cent. Of the 228 patients discharged improved, 25 per cent of the infants died since operation, whereas only 2 per cent of children died and 3 per cent are not doing well; thus, 95 per cent of the children who were greatly benefited maintained their improvement.

DISCUSSION

Dr. Philip E. Rothman, Los Angeles: What is the explanation for the left axis deviation?

Dr. Helen B. Taussig, Baltimore: Left axis deviation occurs overwhelmingly with atresia of the tricuspid valves and defective development of the right ventricle.

Of those who have been studied at autopsy, 2, I believe, showed atresia of the tricuspid valves. It is true that 2 of the children who died after operation had left axis deviation. I think the difficulty was in getting the blood from the right auricle to the common ventricle, since the opening for the flow before operation was so small. Even after operation circulation could not be maintained indefinitely. In particular, the trouble is defective development of the left ventricle, and the main circulation must be carried on by the right ventricle.

Treatment of Patients with Fibrosis of the Pancreas. Dr. Charles D. May, Dr Charles U. Lowe and Dr. Charles A. Janeway, Boston.

This paper will be published in full in a later issue of the American Journal of Diseases of Children.

DISCUSSION

Dr. Dorothy K. S. Anderson, New York: Dr. May, in your opinion, is the respiratory difficulty these children have purely on a congenital basis in regard to changes in the bronchi, or is it due to a deficiency, not necessarily in vitamin A, but to some nutritional deficiency?

I have felt, on the basis of the last few years' experience, that the cause was a nutritional deficiency in large part because of the increasing group of children who have never had bronchitis—the oldest of them is now 7 years of age—and who have been on a special diet, not restricted in calories, but primarily restricted in fat. Eggs are included in the diet. I have now 10 or 11 patients over 1 year of age who have never had a sign of bronchitis.

Dr. Charles Hendee Smith, New York: I should like to ask Dr. May whether the banana is discarded as a substitute for other carbohydrates, or whether its use is taken for granted in his statement.

Dr. Charles D. May, Boston: Dr. Anderson's question in regard to the nature of the pulmonary lesion, from the pathologic point of view, should obviously be left to Dr. Sidney Farber to answer. It is my impression and understanding of what he has taught us that the lesion could well be existent from birth, appearing almost as early as the pancreatic lesion and of a similar nature basically.

We have not felt we could prevent the onset of pulmonary symptoms by maintenance of nutrition. On more than one occasion we have observed a well nourished child in whom developed all the classic manifestations of the pulmonary process. The process is likely to develop and to be as apparent in the well nourished as in the malnourished child, for the nutritional status fluctuates independently.

As to Dr. Smith's remarks, I am always most pleased when celiac disease can be excluded entirely from discussions on fibrosis of the pancreas. I think the conditions have no more relation than other diseases which have a single symptom in common. In fibrosis of the pancreas the digestive juices are excluded from the duodenum, a situation the exact opposite to that in celiac disease, in which they are present in abundance. As to tolerance to specific carbohydrates in fibrosis of the pancreas, we have no data regarding clinical expectations. We have no basis for choosing or excluding a single type of carbohydrate.

Multiple Congenital Malformations. Dr. Josef Warkany, Dr. Caroline Roth and Dr. J. G. Wilson, Cincinnati.

The medical literature of the past five decades is replete with statements that multiple congenital malformations are always and necessarily due to changes in the germ plasma.

It is timely to reconsider this statement in the light of recent experiments in which multiple congenital malformations were induced by maternal deficiency in vitamin A. Female rats maintained and bred on a diet deficient in vitamin A gave birth to young, many of which had multiple congenital anomalies. The most frequent anomaly was a retrolenticular membrane which occupied the place of the corpus vitreum. Other defects, such as folding and coloboma of the retina, rudimentary development of the iris and ciliary body and "open eyes," were also observed. Further examination of the animals with the abnormal eyes showed that the pleural cavity did not extend forward to the sternum and that the lungs were underdeveloped. The muscle of the heart had a spongy appearance, and in a number of abnormal animals a diaphragmatic hernia was observed on the right side. Sections through the abdomen showed numerous anomalies in the genitourinary system. The renal pelves and the ureters were not dilated as in the normal animals, and the testes were often not descended. In some of the animals the lower ends of the kidneys were fused so that a horseshoe kidney was formed. The development of the urogenital sinus was retarded and ectopic ureters were observed. Identical malformations were seen in the abnormal young of two strains of rats. Control animals whose mothers were fed an adequate diet did not show these anomalies.

The production of a syndrome of congenital anomalies of the eye, the heart, the respiratory organs, the liver, the kidney and the ureter by maternal deficiency in vitamin A should make one wary of attributing all types of multiple congenital defects to changes in the germ plasma.

DISCUSSION

DR. BENJAMIN KRAMER, Brooklyn: How late into the course of pregnancy is this diet given? Is there any time at which a change to normal diet would reverse the process?

DR. S. VAN CREVELD, Amsterdam, Netherlands: Since the liberation of Holland, my colleagues and I have been looking for the occurrence of congenital malformations as a result of the long-lasting period of starvation. Interest in this problem was greatly increased when Dr. Clement A. Smith came to Amsterdam and told us of the important results of recent studies of Dr. Warkany. It soon developed that the conditions in rats could not be compared with those in our pregnant women, whose intake of food could not be controlled during the whole time, day and night, of the pregnancy.

We made, however, some observations which might be of importance in relation to the problem. Some years ago we observed a case of fetal keratomalacia in a child of a mother 16 years of age, who during the entire time of pregnancy had poor diet, especially in regard to vitamin A and protein. In addition to fetal keratomalacia, the child had microcephalia, with short hands and feet and multiple telangiectases.

Another child of a mother who had a poor diet during pregnancy showed a combination of malformations much like those described by Dr. Warkany: a cleft palate, hypoplastic mandibles, synchelia and short legs.

Furthermore, in 5 cases we observed lacuna skull and craniofenestria of a type we had not seen for many years in the pediatric clinic. In each case the mother had had a poor diet during pregnancy. In the first year after liberation 2 cases of pancreatic fibrosis were observed in 2 brothers whose mother had a gastric ulcer and during each pregnancy made regular use of liquid petrolatum which decreases the resorption of vitamin A.

I am convinced that these are only isolated observations which may, however, have some interest in connection with the important observations of Dr. Warkany.

DR. JOSEF WARKANY, Cincinnati: Dr. Kramer, these animals were given from the time of weaning a diet almost free of vitamin A. To the basic diet, 2.5 micrograms of carotene were added daily. This carried the animals along but did not permit them to store vitamin A.

When the female rats bred, they were put on a diet completely free of vitamin A and carotene. On this diet they did poorly. Many resorbed or began to resorb their young.

We tried to reverse the changes without success. It seems that those fetuses which are abnormal cannot be brought back to normal by late improvements in the diet; if changes are made too early, normal young result. We have no large experience with experiments in alternating diets, and we do not know the critical period of determination of the abnormalities.

Dr. van Creveld told you that we all think human conditions rarely resemble the conditions of our experimental animals. I am able to give you a quantitative comparison of these conditions, thanks to the work of B. Jackson and V. E. Kinsey, of the Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston. As I told you, these authors observed that the vitamin A level has to be under 12 international units in the mother or no abnormalities occur. In the various nutritional surveys in this country, even in badly fed populations, the vitamin A level was hardly ever reported to be under 50 international units; therefore, we cannot expect any of these anomalies to occur in this country in man unless a pathologic condition of the mother should reduce the vitamin A level. Dietary conditions are probably not sufficiently poor to produce anomalies.

It is interesting that Dr. van Creveld mentioned lacuna skull. I have read three articles on the results of famine due to the war, one from Greece (Valaoras), one from Holland (Dr. C. A. Smith) and one from Russia. Antonov, in Russia, described the effects of the famine during the siege of Leningrad and, like the others, he reported chiefly sterility and miscarriages and some defects in the children of mothers who starved. He also saw mothers who easily produced normal children. Some of these women were cooks or had other jobs connected with food supply, explaining the fact that even in times of famine normal children are born. He also described several children with softness of the skull which is perhaps the same thing that Dr. van Creveld saw. He did not call it lacuna skull, but it would be interesting to determine whether it was the same anomaly.

CHICAGO PEDIATRIC SOCIETY

H. William Elghammer, M.D., *President*

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Nov. 18, 1947

Diabetes and Pregnancy, Its Effect on the Fetus, Infant and Child. Presented by DR. PRISCILLA WHITE, Boston.

DISCUSSION

DR. ROLLIN T. WOODYATT: I consider it an honor to be asked to participate in the program of this society, with Dr. White as the speaker. She has spoken of prediabetes, or potential diabetes. The use of these terms implies a distinction between prediabetes, or potential diabetes, and the diabetic state (or manifest dia-

betes). The essential criteria of the diabetic state are hyperglycemia and glycosuria. When these are present one speaks of manifest diabetes. When they are not, one cannot speak of that condition. I feel that the evidence is practically conclusive that when a patient has true diabetes in early or later life it was predetermined, before he was born. He was not born with diabetes, but with a physiologic structure that was destined to break down at some time in life. What was wrong with the structure? If one could answer that question one would have made much progress in learning the causes of diabetes. For that reason I feel that a study of this type is particularly valuable from the theoretic point of view, aside from the immediate practical import.

In the past ten years I have made it a practice to ask persons with diabetes about weight at birth and the weight of other siblings and relatives. I was impressed some years ago by the occurrence of the disease in a boy of 15, weighing 160 pounds (about 72.6 Kg.) or more. He had weighed 12 pounds (about 5,443 Gm.) at birth and now had diabetes. His sister had weighed 15 pounds (about 6,804 Gm.) at birth. The mother said that she herself had weighed 15 pounds at birth and in her sisters' and brothers' families there were many large babies. Still, the boy was the only one in whom, until that time, diabetes had developed. "Large babies are fruits that grow on the diabetic family tree." It does not follow that any large baby is destined to have diabetes or that any person with diabetes was a large baby at birth. I am sure, however, that the incidence of large babies in families in which there is a history of diabetes is related to whatever it is which one inherits for potential diabetes. All these other anomalies described by Dr. White point in the same direction.

As to the management of pregnancy in diabetes, it was only a year ago that I first tried the hormonal therapy described in the paper. I have treated 4 patients since then. Treatment in these 4 has been successful. Two of the 4 patients were born with large hearts and required oxygen for a few days, but they are getting along well now. This series is too short to permit comparative studies of fetal mortality with this treatment and with the methods formerly used.

From the practical point of view there are some drawbacks in the method. The methods available for estimation of hormones in the blood and urine leave much to be desired. The Astwood modification of the Vanning and Brown method for the estimation of urinary pregnandiol glycuronate is lengthy and inexact. Control estimations on the same specimen of urine with artificially added glycuronate may vary 100 per cent. The limits of error are so wide that two analyses of the same urine may yield figures above and below normal. Biologic assays of estrone in the blood are also elaborate and inexact. Estimations of the 17-ketosteroids by spectrophotometry with infra-red light are said to be much better. But the spectrophotometer required for the purpose is an expensive apparatus, and one must be trained to operate it. My colleagues and I have recently obtained the instrument and hope to have it in operation within a short time. In the meantime we have given diethylstilbestrol and progesterone without accurate assays of the blood and urine. Another drawback, which has been mentioned in previous papers by Dr. White, is the cost of the material employed in treatment. This may amount to $300 in a single case. Some fund would have to be established to make it available for many patients of limited means.

However, as I have stated, I am interested in this work. Our own experience with the method is too limited to permit us to draw definite conclusions, but so far the results have been in harmony with those reported by Dr. White.

DR. ARTHUR COLWELL: It seems like "gilding the lily" to discuss Dr. White's comprehensive paper. However, my co-workers and I have followed her experi-

ence with this large group of pregnancies in women with diabetes with a great deal of interest. It is unusual for one person to have the opportunity to study 300 or 400 consecutive patients, as she has done. Any one who attempts to criticize her methods should present evidence which demonstrates as good results in rates of toxemia and fetal survival as she has shown. Otherwise her methods should be employed.

Dr. Grier will report our experience in the small group of cases in which we have used hormone replacement therapy. Our experience has been favorable and confirmatory. When the incidence of preëclampsia can be reduced from 50 to 5 per cent by sex hormone therapy and the fetal survival rate raised from 50 to 90 per cent, with a large control group for contrast, it seems to me that every physician who assumes the care of a pregnant woman with diabetes is obligated to use such methods until some one presents a method which is equally effective and proved so by adequate controls.

As most of us know, management of diabetes in a pregnant woman presents no difficulty with modern technics with diet and insulin. It has been our experience that the need for insulin increases about 50 per cent, on the average, during pregnancy. It then decreases rather sharply immediately after delivery.

I should like to raise two questions for Dr. White's consideration. Has she had any recent experience to report from the use of stained vaginal smears as a method of judging the adequacy of hormone replacement therapy?

Also, in contemplating her interpretation of the reasons for the improvement in rates of toxemia with treatment, it seems that it should be possible to sterilize a female animal and, by administering large doses of chorionic gonadotropin, produce the equivalent of toxemia seen in untreated abnormal patients. Does Dr. White have any comment to make on this possibility?

Dr. Cecil Draa: In our clinic, my co-workers and I have encountered the problems confronting the patient with diabetes who becomes pregnant in about the usual degree of frequency reported in the literature. The first problem is increased incidence of vascular disease and so-called preeclamptic toxemia. The usual toxemia which develops in these patients, in our experience, seems to be more of a vascular type; rarely have we seen the true eclamptic type, although these patients are not immune to true toxemia of pregnancy, variations in sugar tolerance, increased tendency to ketosis, instability of diabetes during labor and post partum. The second problem is in fetal complications, such as the increased rate of early abortions, sudden intrauterine death near term, early onset of spontaneous labor, increased size of the baby, polyhydramnios and congenital anomalies.

In our clinic to date, we have met this problem by close cooperation between internist, pediatrician and obstetrician. We feel that the patients with diabetes should have careful management and control of general nutrition, frequent prenatal visits and attention paid to the general physical status of the patient in the elimination of foci of infection, care of anemia and close observation, with hospitalization if necessary, when there are signs of toxemia or vascular disease. About three weeks prior to term, these patients are hospitalized for stabilization of diabetes and determination of the type of delivery. During labor they are treated on an emergency schedule by the diabetic service, and this is continued post partum until diabetes is stabilized. After delivery, the babies are immediately placed in the care of the pediatric service.

We have not found it necessary to induce labor unless it is specifically indicated by the general condition of the patient or by obstetric conditions. I feel that adding a prematurity factor to a baby already below par physically will eventually lead to less favorable results. We have reserved cesarean section, which is so frequently

advocated to get a live baby, for patients with definite obstetric indications, such as cephalopelvic disproportion, placenta previa, previous history of stillbirth and progressive toxemia. I have often wondered how many babies were saved by early cesarean section who might otherwise have died during labor or just before onset of labor. I feel that these babies are fundamentally in poor physical condition and probably would die whether cesarean section was performed or delivery was normal. Cesarean section is not a panacea, since it is known from reviewing statistics that the fetal death rate is high.

We have employed hormone therapy in patients with diabetes infrequently. We have not made hormone assays for these patients, but hope to carry on this type of work in the near future. After reviewing the conflicting reports of Taylor and his co-workers, Smith and Smith and Dr. White, and after considering our experience with the clinical use of hormones in other gynecologic conditions, we hesitate to subject the patient to the expense of intensive hormone therapy. I feel that it should be emphasized that hormone therapy must be limited to those patients in whom it is definitely indicated, that is, to those who, in assays of chorionic gonadotropin and estrogens, show the pattern described.

The following information is pertinent in the 5 cases in which fetal death occurred:

CASE 1.—The woman was 41 years old; this was her tenth pregnancy, and she had had seven children. Diabetes was observed in the thirty-second week of pregnancy, and delivery was one month premature. The period of labor was forty-six hours, and the infant, who weighed 5 pounds, 11.5 ounces (about 2,580 Gm.), lived one hour. The patient had advanced hypertensive cardiac disease, and on admission to the prenatal clinic her blood pressure was 200 systolic and 120 diastolic.

CASE 2.—The woman had had three pregnancies and two children. The first pregnancy was normal, and the second pregnancy resulted in a stillborn infant of 8 pounds (about 3,629 Gm.). The Rh factor was observed to be negative, and she had had diabetes of a mild nature for three years. Delivery was one week past the expected date, with craniotomy for hydrocephalus. The baby weighed 11 pounds 5 ounces (about 5,131 Gm.). Autopsy revealed cerebral atrophy from pressure. There was decided hematopoiesis. Myeloid eosinophilic infiltration, hyperplasia and hypertrophy of the islands of Langerhans and excessive glycogen in the liver were observed.

CASE 3.—The woman was a primipara, aged 23. Diabetes was of eight years' duration. The antepartum period was normal until one week before the onset of labor, at which time the patient had an attack described by her as an insulin reaction. The following day she did not feel life, and examination revealed no fetal cardiac tones. The baby weighed 7 pounds 9 ounces (about 3,430 Gm.). Postmortem observations were indefinite as to the cause of intrauterine death.

CASE 4.—The woman had had two pregnancies and had given birth to one stillborn child. Diabetes was of nineteen years' duration and was severe. The patient went into labor spontaneously in the seventh month. She was delivered of a female infant, 3½ pounds (about 1,588 Gm.), that lived for a few hours. The cause of death was prematurity.

CASE 5.—The woman had had two pregnancies and had given birth to one child. The previous pregnancy was of eight months' duration. The infant lived for one hour. The patient had had diabetes for three years. Ante partum she was normal except for edema one week before delivery. Labor was spontaneous in

the seventh month. The delivery was normal, with breech presentation. The infant weighed 5 pounds 13 ounces (about 2,637 Gm.), and the condition at birth was poor. The infant lived for a few hours. Postmortem observations indicated prematurity to be the cause of death.

Tables 2 and 3 include data supplementary to that in table 1.

TABLE 1.—*Analysis of Patients with Diabetes Delivered on the Obstetric Service at Presbyterian Hospital in Five Years*

Total Number of Deliveries	Number of Patients With Diabetes	Number of Fetal Deaths	Duration of Disease: Ten Years or Under (Number of Patients)	Duration of Disease: Over Ten Years (Number of Patients)	Number of Patients With Diabetes During Present Pregnancy
6,599	43	5	16	28*	9

* The longest duration was twenty-one years.

TABLE 2.—*Types of Deliveries*

Type	Number of Cases
Normal delivery	22
Cesarian section	9
By forceps (low)	11
Craniotomy	1

TABLE 3.—*Indications for Cesarean Section*

Indications	Number of Cases
Previous cesarian section	1
Placenta previa	1
Cephalopelvic disproportion	5
Toxemia	2

DR. ROBERT GRIER: The individual obstetrician's experience with pregnant patients with diabetes is limited. Reports such as Dr. White has given are phenomenal. A review of cases of such disease at the Evanston Hospital for the past twenty years revealed only 18 in 22,246 cases of pregnancy. In the first ten year period (1928 through 1937) only 4 women who had diabetes were delivered. Since the total number of cases of pregnancy was 9,228, the incidence was 1 in 2,307. In the past ten years my co-workers and I have delivered 14 pregnant women with diabetes. Thus, in 13,018 pregnancies the incidence was 1 in 930. In the former group, only 1 woman was known to have had diabetes for more than two years. In the latter group, 1 was known to have had diabetes for three years, and the rest of the patients were known to have had it for from five to eleven years.

Oddly enough, the number of live births in the first ten years was 3, or 75 per cent. I doubt whether our records of abortions in patients with diabetes for this period are accurate. All these women were more than 28 years of age; the average age was 31.5 years.

In the last ten years, 5 pregnant women with diabetes had termination of their pregnancies before viability was demonstrated. In 3 women termination was spontaneous, and in 2 there was therapeutic abortion. Eight patients had viable

babies, and 6 of the babies lived, an incidence of 75 per cent. The average age of the patients was 28.3 years; the youngest was 20 and the oldest 39 years of age.

During the past year, following Dr. White's recommendation, we have given the women diethylstilbestrol and progesterone, starting early in pregnancy. Of 4 such patients there was abortion in none. There were 3 live healthy children. The infant who died was an unusually large child, weighing 4,220 Gm., who died nineteen hours after birth. We think that the neonatal management in this case was inadequate and that the child might have been saved. This again is an incidence of live births of 75 per cent, and there were no abortions. All women were delivered by cesarean section at the thirty-seventh or thirty-eighth week of pregnancy under spinal anesthesia. In this small series of cases the results are encouraging.

TABLE 4.—*Data Relative to Toxemia*

Condition	Number of Cases
Preeclamptic toxemia with hypertension, albuminuria and edema	7
Edema only, of varying degree	9
Hypertension	4
Occasional albuminuria without hypertension or edema	1
No evidence of toxemia	22

TABLE 5.—*Onset of Labor*

Occurrence	Number of Cases
Medically induced	4
Spontaneous	39
At term	19
Premature, 2 weeks	13
Premature, 4 weeks	7
Premature, 8 weeks	4

TABLE 6.—*Severity of Diabetes*

Degree of Severity	Number of Cases
Severe	18
Moderate to severe	13
Mild	12

Smith of Boston has recently reported that giving diethylstilbesterol to a pregnant woman would increase the output of pregnandiol in the urine. However, Davis, of Lying-in Hospital in Chicago, has recently refuted this statement. If Smith is correct, then could not the use of diethylstilbesterol alone save the patient the expense of progesterone? I wonder whether the doses of progesterone which are given, expensive as they are, are not infinitesimal when compared with the large amounts observed in the blood serum during pregnancy. The large series of cases reported by Dr. White, with a rate of infant survival of more than 90 per cent, has not been equaled by any one. Consequently, I shall continue to follow her plan of treatment.

DR. HEYWORTH N. SANFORD: I feel that the society is fortunate in being able to hear this interesting paper. There is one thing that I would like to emphasize, which Dr. Grier has already mentioned, and that is that diabetes in pregnancy is

not a frequently seen entity. Potter estimated that in a general hospital the incidence is about 1 in 1,000. Dr. Grier stated that the incidence was about that and is increasing. I believe that there is not a greater incidence of diabetes in mothers but that there are more internists interested in diabetes. I have been fortunate in being associated with Dr. Woodyatt at Presbyterian Hospital, who has a larger group with diabetes than one ordinarily sees.

I would like to review the frequency with which we have observed diabetes associated with fetal deaths. In five years at Presbyterian Hospital, with 6,500 deliveries, there were 43 mothers with diabetes, an incidence of about 0.6 per cent, or about six times more than one would see in the average general hospital. In this group there were 5 fetal deaths, stillbirths and neonatal deaths, a rate of mortality of 12 per cent, which is comparable to Dr. White's rate of mortality of 10 per cent. During this period, stillbirths and neonatal deaths in the group of more than 6,500 deliveries constituted approximately 3 per cent. In other words, in the cases in which the mother had diabetes there was a rate of fetal mortality four times that for normal mothers.

Pediatricians simply accept the by-products of the combined work of internists and obstetricans in the babies of mothers with diabetes, and I have felt that these babies fall roughly into three groups. In the first group are babies in whom the condition is severe; fortunately, this group is small. I have been unable to observe any correlation between the incidence in this group and the severity of the maternal diabetes. In this small group there is a high rate of mortality, most of the babies dying in twenty-four hours. The pathologic observations are of interest. Many are prematurely born, and they have certain characteristic—hyperplasia of the islands of Langerhans and adrenal glands and erythroblastosis. I object to the term "pseudoerythroblastosis"—the disease is either present or not present. There is no difference between erythroblastosis seen in these babies and that seen in babies with sepsis, congenital syphilis or hemolysis, as with the Rh factor. There seems to be an impression that erythroblastosis that does not originate from the Rh factor is not true erythroblastosis. The only difference is in the eosinophilic elements, which are excessive in babies of mothers with diabetes. Miller claimed that their infiltration into the anterior lobe of the pituitary gland is the characteristic pathologic aspect. This is not observed in other forms of erythroblastosis.

In cases of moderately severe disease the babies may be normal size or larger than normal size. They also have evidence of erythroblastosis in an excessive number of circulating nucleated red cells. One of the highest percentages that we have seen was 38 per cent of nucleated red cells for the first three days of life. The baby lived and was apparently normal. In babies of mothers with diabetes this is a characteristic observation and is associated many times with the other deformities mentioned. About 10 per cent also have dilation of the heart in all dimensions. This can be shown easily fluoroscopically and roentgenographically. We also see certain peculiarities, such as right axis deviation, sinus tachycardia and the T wave diaphasic in lead I. If these are included, there will be abnormal observations in almost 20 per cent of cases. The cardiac hypertrophy decreases rapidly and is entirely gone in two weeks. The symptoms observed electrocardiographically disappear more slowly, but sinus tachycardia and right axis deviation persist for many months.

The third and largest group usually show no abnormalities. The babies may be large or normal. There are certainly no observations to indicate any abnormality.

I believe that the treatment advocated is good. I would make one suggestion; while the blood sugar is unstable and this observation cannot be used to determine whether or not the baby has hyperglycemia, occasionally an infant has hypogly-

cemia. For this reason these babies should be given dextrose after delivery. First, aspiration is performed, then ½ ounce (about 14 Gm.) of 50 per cent solution of dextrose is given by gavage tube, and in two hours 1 ounce (about 28 Gm.) more is given. I do not like to give these babies injections; there is always a chance for infection and complications, and when the dextrose is given in this manner the same thing is accomplished as when it is given subcutaneously. The baby is then given oxygen for twenty-four hours or longer. We have not had much difficulty in these cases after forty-eight hours. All the deaths have occurred within that period. If the baby survives for forty-eight hours, the chances for survival are good. These babies are given the routine treatment for the newborn —nothing by mouth except water and breast feeding immediately, with no other feeding given for seven or eight days. Thus, a crude form of dehydration is accomplished. At the end of seven days the baby's weight and the amount of breast milk obtained are observed, and if supplementary feeding is necessary it is given.

Dr. White stated that after the "newborn period" many of these babies showed excessive weight. I have not observed that. I believe, therefore, that the pediatrician receives the by-products of obstetric and medical care and that the life of the baby is gained or lost before the obstetrician ever obtains control of it.

DR. A. L. NEWCOMB: I want to comment on Dr. Sanford's point about hypoglycemia. About eight or ten years ago, a baby, born spontaneously about 3 p. m., had a violent convulsion about 10 p. m., with blood sugar below 30. The baby recovered from convulsions, but the baby was spastic thereafter. I suppose that the damage to the brain was due to anoxemia secondary to hypoglycemia due to insulin.

Dr. Gideon Wells gave me a slide of a precipitately born infant who died from convulsions shortly after birth. Diabetes was undiagnosed in the mother, who had attended the clinic for the first time that day. The extraordinary hypertrophy of the islands of Langerhans in this infant might, because the diabetes was untreated in the mother, be explained by excessive demand by the maternal metabolism. In the treated mother with diabetes, the insulin demand would be supplied exogenously and fetal hypoglycemic convulsions might be expected to be infrequent.

DR. PRISCILLA WHITE: There are several points that Dr. Woodyatt discussed that I would like to emphasize. The methods of hormone assays are not completely satisfactory. The normal pattern has not been established to the satisfaction of chemists. One of the government projects, which it is hoped will be carried out this year, is the determination through chemistry of the hormone pattern of pregnancy, which is really needed before studies are continued.

In answer to Dr. Colwell, I believe that producing toxemia in animals in experiments is one of the most difficult things to do. Experiments have been done on rabbits and guinea pigs, by which pregnancy was prolonged and live fetuses were produced. I think that some one has produced eclampsia in rabbits; it is extraordinarily difficult.

The vaginal smear technic, which I hoped would help, has not proved satisfactory. If observations were abnormal, they were consistent with an abnormal pregnancy, but the test is a delicate one and it does not rule out trouble. The toxemia seen in pregnancy in women with diabetes would not be of too much value, in my opinion, but Dr. Titus feels that it is not what one sees normally. He feels that one of the differences is in the early period, in which rapid gain of weight occurs. I think of it as disturbance of water metabolism. He has based the duration of pregnancy on whether the cervix is effaced rather than on the expected date. I hope to get more normal infants.

I note that in Chicago, as in Boston, the obstetrician worries about diabetes and the internist about toxemia of pregnancy. The incidence of diabetes is low, based on the number of women in the childbearing age. One would expect 1 in 1,000 to have diabetes. In large obstetric hospitals 3 to 6 are expected in a year. In our large clinic, my co-workers and I never have less than 25 under observation at one time.

I would like to ask whether, from the obstetrician's point of view, when one uses hormones in pregnancy for other conditions, one may have intrauterine death. Dr. Fraser of Montreal, Canada, asked whether that was another argument for using cesarean section. I think that one can use diethylstilbesterol in enormous doses without harm. In 1940 we tried to treat a group with diethylstilbesterol alone. Certainly, there were no side reactions.

I was interested in the comment about breast feeding. We did not believe that our patients lactated normally, and, of course, with diethylstilbestrol they do not lactate. Most of the patients are given protamine insulin, and the last dose is given twenty-four hours before delivery. The mother does not receive dextrose in the immediate predelivery period, which may protect the infant.

The technic for roentgenographic observation of the pelvic arteries is the simple technic used for bone; if injections were used, there might be more indicative observations.

Book Reviews

Advances in Pediatrics. Edited by S. Z. Levine, A. M. Butler, L. E. Holt Jr., M.D. and A. A. Weech. Volume II. Price, $6.75. Pp. 409, with several Illustrations. New York: Interscience Publishers, Inc., 1947.

The practicing pediatrician, as well as the man in teaching and research, will find this an excellent book. In studying the book carefully, the reader not only will learn what is new in the field of pediatrics, but will also be able to apply this knowledge in his daily practice. The subjects are well selected for their timeliness and importance and are discussed with sufficient thoroughness to give more than superficial information. The presentation of the subjects of most chapters offers stimulation and guidance for further research, and the authors are outstanding authorities in their fields.

The chapter on the "Etiology of Congenital Malformations" presents for the pediatrician a discussion of a new field—new at least for this specialty. Although it is highly interesting reading, its detailed treatment seems to have little value to the practicing pediatrician. Its implication of future usefulness in preventive medicine probably applies rather to the field of obstetrics or of general practice, since the pediatrician is confronted with the finished product after etiologic influences have done their permanent damage. The description of a new disease, "Acute Infectious Lymphocytosis," not only will be actual news to many readers but will probably furnish an explanation of previously obscure hematologic cases. The clinical and laboratory features are described, and a careful evaluation of the differentiation from other conditions is made. The report on the "Role of Fluorine in Dental Caries" attracts the practitioner's attention to a virgin field of preventive medicine and/or dentistry. Little has been written on this subject in the pediatric literature, although the pediatrician not only is vitally interested in maintaining good dentition in his young patients but also is interested in the possible influences of this preventive medication on the growing organism.

The article on "Purulent Meningitis" is of utmost value to the practitioner. The complete outline of management of purulent meningitis will aid every one as a quick reference in the treatment in individual cases. The discussion on dosage and route of administration of chemotherapeutic agents overlaps partly the succeeding chapter on "Chemotherapy," which offers practical discussions on the present status of antibiotic substances. The paragraph on streptomycin is short, and recent reports in the literature give more complete information than the book. "Atypical pneumonia," a new and little known clinical entity, is described in textbook fashion, and understanding is facilitated by the addition of case reports and roentgenograms. One hundred and ninety-seven references give the interested reader material for further study. A thorough discussion of "Endocrine and Other Factors Determining the Growth of Children" under physiologic and pathologic conditions follows. The anterior lobe of the pituitary gland and the thyroid gland, the gonads and the adrenal cortex are discussed in their normal action and under conditions producing hyperfunction or hypofunction. The interaction of the glands is taken up specifically. Only a short paragraph is dedicated to the influence of the central nervous system on growth. The problem of nutrition and growth is outlined in a final paragraph, and the reader is referred to more detailed studies

on the subject. In presenting this involved problem, the solution to which is still in the experimental stage, not much practical help is offered. Although from a therapeutic point of view the article on "Virus Diarrhea" does not make any contribution, it describes in brief the work done by the author and by others on this harrassing problem of the pediatrician. It seems established that in at least some of the cases of diarrhea of the newborn the causative agent is a virus and that the infection confers immunity to test animals. This discovery may lead to means of specific therapy or prevention. The chapter on "Prematurity" brings together all the newer developments in that field and thus covers considerable territory. However, its concise form makes one doubt whether the practicing physician will be able to make use of it in his work without considerable further reading. The highly technical article on "Genesis of Physiologic Hyperbilirubinemia" offers a good insight into some physiopathologic events of the circulatory system and the liver of the newborn. New avenues are opened for the explanation of the age-old observation of physiologic jaundice. "Prevention of Recurrence of Rheumatic Fever" is a short review of some of the more promising methods in this field which were investigated during the last years. Less popular methods are not described. The author discusses in detail her observations at the Irvington House involving the use of sulfanilamide, sulfamerazine, sulfathiazole and sulfadiazine and penicillin.

The understanding of the book is aided by illustrations, graphs and tables. Extensive bibliographic references, arranged according to content and alphabetically, give the investigator a good basis for further study.

Child Health. Published on Behalf of the Practitioner. Edited by Alan A. Moncrieff, M.D., F.R.C.P., and W. A. R. Thomson. Price, 14s. Pp. 254. London: Eyre & Spottiswoode, Ltd., 1947.

In view of the growing tendency in England to give greater attention to the medical care of children in health as well as in sickness, and of the call for general practitioners to participate more actively in health services for children in the future, a number of authorities in England were asked to contribute chapters to provide for practitioners a book dealing with the problems of child health and the services required for children's care. This book attempts, first, to familiarize the practitioner with the organization and functions of various types of services for children and, second, to present the common problems with which the physician must deal in conducting these health services and the appropriate methods of doing so.

The book is of interest to American pediatricians because of the chapters concerning the organization of child welfare centers, preschool child clinics and school health services and the differences in the procedures in the two countries which they reveal. The chapters on nursery schools, residential schools for handicapped children, care of the crippled child, the child guidance clinic, the deaf child, the blind child and physical education are the most unusual ones for a medical text and should be of interest and value to British physicians. Of much less interest, and of more variable quality, are the chapters dealing with the common problems of young children and the advice and management offered in health services. The chapters on juvenile rheumatism and tuberculosis, on breast and artificial feeding and on diet for the school child are of necessity too brief and superficial to afford the practitioner a sound background of knowledge on which to advise in these matters. From the American point of view, one misses especially a consideration of the factors of immaturity and growth, which provide the foun-

dation for understanding these problems and the justification for the recommendations made.

The introduction to this volume, by Sir Leonard Parsons, is undoubtedly the most interesting part to the pediatrician because of its recommendations for pediatric education and practice and for the organization of child health services and medical care. Parsons' appeal for more instruction in pediatric subjects, more experience with children for medical students and more participation by the family physician in medical care and in child health services is most timely. It is of interest, however, that he does not mention the need for training in respect to human growth and development as the groundwork for care of children, and this is given no attention in any part of the book. Most American pediatricians would doubtless frown on Parsons' suggestion that in group practice general practitioners showing special interest in and skill with infants and children might come to be recognized as the pediatricians of their group. Since pediatrics is a specialty with many aspects in which basic training is required, the best road to its practice would seem to be that of several years of organized, supervised and intensive work with well and sick children, following a good general medical education.

Introducción al estudio de la plasmoterapia. By José M. Massons. No price listed. Pp. 276, with 15 diagrams. Barcelona, Spain: Miguel Servet, 1947.

This monograph is a well organized résumé of the subject, clearly written and well documented by references to a large international bibliography.

Part 1 is concerned with the history of blood transfusion and of the origins and development of plasmotherapy; part 2, with the chemistry and physiology of plasma and with clinical conditions in which there are alterations in plasma relations; part 3, with a discussion of the various substances used for "blood substitutes" in therapeutics, and part 4, with indications for plasmotherapy and the technic of administration.

Of particular interest is the discussion of the author's own work on the use of animal plasmas rendered nonanaphylactic by treatment with formaldehyde and other processes. He cites his experimental work to confirm the safety of this material and refers to Morais and Moreira as having used these plasmas successfully in the clinic. No clinical details are given. Of course, such data had been better given, since this investigation is an extremely important piece of work, if its results could be confirmed.

The only weak point in the monograph is the omission of consideration of the acid-base balance. This subject would appear to be an important one, especially in relation to the use of plasma in acute nutritional disturbances in infants.

This work is a good general review of plasmotherapy and is recommended to pediatricians and to internists interested in the subject.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.
Place: Stockholm. Time: Aug. 10-16, 1948.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandsche Vereeninging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft für Pädiatrie

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

Sociedad Boliviana de Pediatria

President: Prof. Dr. Luis V. Sotelo.
Secretary: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Place: Casilla de Correos 12, La Paz, Bolivia.

Sociedad Chilena de Pediatria

President: Mr. Cesar Izzo Parodi, Merced 565, Santiago, Chile.
General Secretary: Dr. Jorge Peña Cereceda, Santiago, Chile.

Sociedad Cubana de Pediatria

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

Sociedad Dominicana de Pediatria

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

Sociedad Ecuatoriana de Pediatria

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

Sociedad Mexicana de Pediatria

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Carlos E. Castillo, Hospital Municipal de Niños, Caracas.
Place: Hospital Municipal de Niños, Caracas.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.
Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Héctor C. Bazzano.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenda Agraciada 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Atlantic City, N. J. Time: June 6-10, 1949.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. John A. Toomey, City Hospital, 3395 Scranton Rd., Cleveland 9.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Areal Meetings:
Place: Seattle, Wash. Time: Sept. 13-15, 1948.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

American Pediatric Society

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Atlantic City. Time: May 3-5 (?), 1949.

Canadian Society for the Study of Diseases of Children

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

Society for Pediatric Research

President: Dr. Sidney Farber, 300 Longwood Ave., Boston.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.
Place: Seattle. Time: Sept. 13-15, 1948.

Northwestern Pediatric Society

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. John M. Nelson, 1558 Humboldt St., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Place: Miami, Fla. Time: October 1948.

STATE

Alabama Pediatric Society

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.
Place: Montgomery, Ala. Time: September 1949

Arizona Pediatric Society

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena, Calif.
Place: Los Angeles. Time: April 1949.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach, Fla.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. F. M. Meyer, 144 Golden Hill St., Bridgeport, Conn.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bdg., Davenport.
Place: Des Moines. Time: April 1949.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SECTION

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.
Place: Philadelphia. Time: Oct. 4-7, 1948.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.
Place: Detroit. Time: Sept. 23, 1948.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Gerald C. O'Neil, 116 S. 49th Ave., Omaha 3.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Jersey Medical Society, Pediatric Section

Chairman: Dr. Robert E. Jennings, 117 Washington St., East Orange.
Secretary: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Samuel Ravenel, 371 N. Elm St., Greensboro, N. C.
Secretary: Dr. Charles Gay, 1521 Elizabeth Ave., Charlotte, N. C.
Place: Roaring Gap, N. C. Time: Sept. 11, 1948.

Northern California Pediatric Society

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

South Carolina Pediatric Society

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.
Place: Columbia. Time: Sept. 13, 1948.

Tennessee Pediatric Society

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

Texas Pediatric Society

President: Dr. Charles B. Alexander, 1716 Nix Professional Bldg., San Antonio 5.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.

Virginia Pediatric Society

President: Dr. Thomas Gibson, 114 W. Boscawen St., Winchester.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

Wisconsin State Medical Society, Section on Pediatrics

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore .
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Harold T. Vogel, 3420—86th St., Jackson Heights, N. Y.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Thursday of each month.

Detroit Pediatric Society

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

Houston Pediatric Society

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville-Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

Memphis Pediatric Society

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

Milwaukee Pediatric Society

President: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2, Wis.
Secretary-Treasurer: Dr. Katharine Baird, 1411 Wauwatosa Ave., Wauwatosa 13, Wis.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

Oklahoma City Pediatric Society

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

Philadelphia Pediatric Society

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Pittsburgh Academy of Medicine. Time: Second Friday in October, December, February and April.

Queens Pediatric Society

Chairman: Dr. Walter C. A. Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

Richmond Pediatric Society

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. V. E. Hrdlicka, 7424 Cromwell Dr., St. Louis.
Secretary-Treasurer: Dr. Don L. Thurston, 21 Cambridge Court, St. Louis 22.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

San Antonio Pediatric Society

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

Seattle Pediatric Society

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.
Place: University Hospital, Ann Arbor. Time: Oct. 29-30, 1948.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).